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The Vascular Access Related Infections: Have We Anticipated Them Adequately?

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The number of patients in need of haemodialysis (HD) is increasing from time to time. In 2018, the Indonesian Renal Registry documented more than 130,000 active patients from 651 registered HD centres. Twenty percent are diabetic patients with end-stage renal disease (ESDR) equal to 8,633 patients.[1] Diabetes Mellitus accounts for 2% of all diabetes cases in the age of 15 year-old and above.[2] Hence, the increasing need for HD is inevitable and is parallel with the need for vascular access procedures.

One of the major problems that occurs with vascular access is the risk of infection. Among HD patients, mortality and morbidity are predominantly associated with infection; about one-fifth as a cause of hospital admissions, one-fourth of the infection-related admissions are due to infection of vascular access. In addition, patients on HD are hospitalized more frequently compared to other illnesses. Therefore, information on the magnitude of the problems needs to be well understood.[3] Susilo et.al,[4] reported around 40% of patients with temporary vascular access had an infection. Data is limited and might be also underestimated.

The definition of vascular access-related infection needs to be carefully classified. The infection site can be classified as: (1) exit site infection, inflammation confined around the skin area at the catheter exit site and not involving the cuff if the catheter is tunneled; (2) the infection of the tunnel, inflammation along the subcutaneous tunnel whereby exudate can be drained to the exit site; and (3) bloodstream infection, with positive blood culture.[5] An agreed upon and unified definition is mandatory for clinical use and research. Challenges for clinicians even start from determining the incidence due to different views on the reporting of such instances, whether the occurrence of infection should be reported as per dialysis session or rate per-patient-day or per-catheter-day. This heterogeneity makes the general picture of the problem needs to be carefully analyzed.[6,7]

Unfortunately, the available studies examining risk factors for vascular access-associated infection are scarce and mostly collected with substandard methodology.[3] Susilo et al.[4] found that female gender, anemia, duration of catheter use, and diabetes mellitus are risk factors for temporary vascular access related infection. However, the vascular access type is also an important factor contributing to bloodstream infection.[4,6]

It is to be highlighted that the study of Susilo et al.[4] may represent the population of a referral hospital for HD, yet as a reader it is worth noting that heterogeneity among centres and populations should be acknowledged. Information is needed on the clinical impact of transient vascular access-related infections such as mortality, which has not been described in this report. A comprehensive in-depth review and further research of these studies are crucial

for a greater level of understanding for the cause of infection and therefore inform effective early detection and prevention strategies to reduce morbidity and mortality among haemodialysis patients, especially at-risk patients.

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The Relationship Between fragmented QRS Complexes (fQRS) and the Severity of Coronary Artery Lesion in Coronary Artery Disease: A Cross-sectional Study

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ABSTRACT

Background: *The severity of coronary artery lesion is commonly used as a predictor of mortality, major adverse cardiovascular event (MACE), and revascularization in coronary artery disease (CAD). Fragmented QRS complex (fQRS) is used as a marker of myocardial ischemia in patients with CAD. The relationship between the two should be studied further. The objective of this study was to determine the relationship between fQRS and the severity of coronary lesion in patients with CAD.* ***Methods****: A cross-sectional study was conducted at Cipto Mangunkusumo Hospital Jakarta. Secondary data were taken from 172 patients with CAD who underwent percutaneous coronary intervention (PCI) from January to June 2018 with total sampling. Patients were divided into two groups based on the existence of fQRS. Demographic, clinical, and corangiography characteristics (Gensini score, total vascular lesion, and vascular lesion significance) were studied. Data were analyzed using agreement test and chi-square.* ***Results****: fQRS was present in 94 subjects (54.6%). Bivariate analysis showed a significant difference between fQRS with mild-moderate Gensini score as well as mild-severe Gensini score (kappa = 0.721 and 0.820; p<0.001), fQRS with significant CAD (kappa = 0.670; p<0.001), and fQRS with multivessel CAD (kappa = 0.787; p<0.001).* ***Conclusion****: There is a significant relationship between fQRS and the degree of severity of coronary lesion in CAD patients.*

Keywords*: coronary artery disease, fragmented QRS, Gensini score.*

INTRODUCTION

Coronary artery disease (CAD) is one of the biggest health problems worldwide. CAD increasing morbidity, mortality and causing significant socioeconomic burden. An estimated 7.4 million (12.9%) deaths are caused by CAD, and it is one of the leading causes of health care cost.[1]

The severity and complexity of coronary artery lesion in CAD patients is commonly used as a predictor of mortality, major adverse cardiovascular events (MACE), and the need for revascularization.[2] Coronary angiography remains a standard diagnostic tool to evaluate coronary lesions. Gensini score is considered the most commonly used and major scoring system

to determine the severity and complexity of coronary lesions.[2-4] Although both the Gensini scoring system and coronary angiography have a lot of advantages, coronary angiography is an invasive procedure available only in certain centers and can be expensive.

Fragmented QRS (fQRS) complexes are novel electrocardiographic signals, which form because of non-homogenous conduction to the area of myocardial ischemic or scar. This causes *zigzag* conduction around the ischemic or scarred myocardium, resulting in the "fragmentation" of QRS complexes.[5,6] fQRS is used as a marker of myocardial ischemia in patients with CAD and can be used to detect coronary lesions.[7] Q waves can disappear over time, and as there is no Q wave formation, fragmented QRS complexes are the only sign of scarring or impaired perfusion in the myocardium.[8] Electrocardiogram (ECG), which detects fQRS, is a tool that is easily accessible, non-invasive, and cost-effective.

In this study, we evaluated the relationship between fQRS and the degree of severity of coronary lesions in CAD patients with different approaches. Instead of using a numerical form like previous studies, the Gensini score has more clinical meaning in categorical form. The division of complexity degree in categorical form can determine the further risk of MACE, prognosis, as well as planning therapy[8,9]. This study will also use a different methodological approach from previous studies, namely not only looking at the magnitude of the effect (significance) but also the strength of the relationship between the two variables with the suitability test. In addition, this study includes both narrow and wide fQRS criteria that have not been carried out in other studies. Moreover, research on this matter has not been carried out on the Indonesian population. The prevalence of CAD events varies by ethnicity and population in Indonesia, including Southeast Asian ethnicities, where the prevalence of CAD is quite high and there are no similar studies in these ethnic groups.[8,9] This has led to a lack of attention regarding the benefits of screening and stratification of the complexity of coronary lesions with fragmented QRS complexes in Indonesia. This study was made to assess the relationship of fQRS on the ECG in identifying the degree of complexity of coronary lesions in CHD patients in Indonesia.

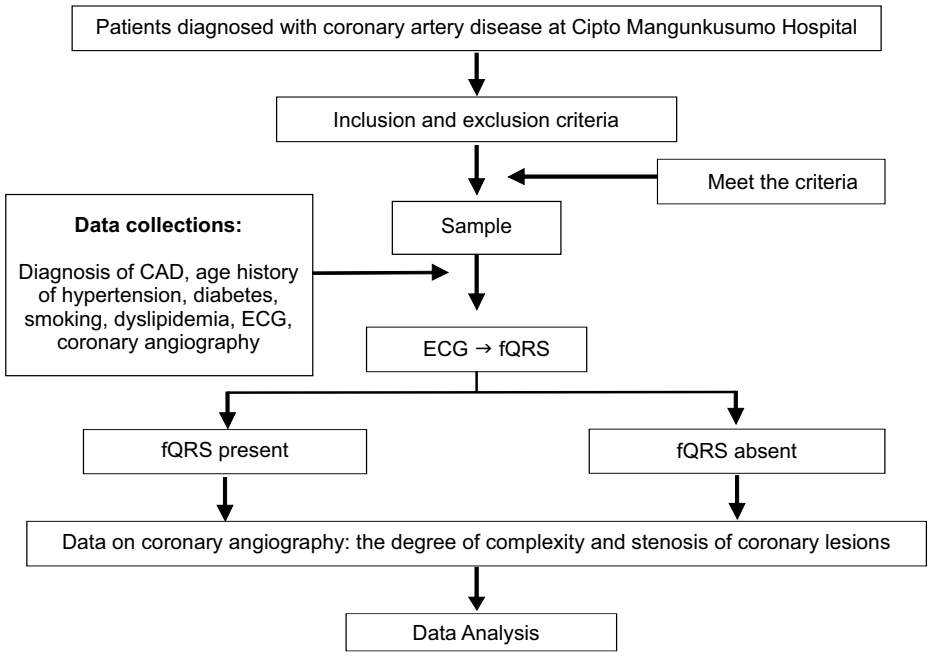

Figure 1. Protocol of the study.

METHODS

Study Design and Population

This study was a cross-sectional study conducted at the Cipto Mangunkusumo Hospital in Indonesia. The subjects of this study were obtained from the medical records of patients with CAD who underwent percutaneous coronary intervention (PCI) at Cipto Mangunkusumo Hospital from January to June 2018 with total sampling. Sample size calculation used two proportions comparison and obtained a minimum sample size of 165 subjects.

The inclusion criteria were patients aged ≥ 18 years diagnosed with CAD via corangiography. The exclusion criteria of this study were incomplete ECG and corangiography data, patients with incomplete right bundle branch block (RBBB) or pathological Q wave, patients with congenital heart disease, ventricular aneurysm, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, or Brugada syndrome, and patients with normal coronary artery with fQRS in coronary territories. The study protocol was approved by the ethics committee of Faculty of Medicine Universitas Indonesia (Reference no. 0442/UN2.F1/ETIK/2018).

Electrocardiography

In the ECG data used, ECG was performed within seven days before the coronary angiography. The ECG examination used the Bionet/Cardiotouch 3000® ECG machine with low pass filter cut off (150 Hz), AC 60 Hz, 25 mm/s, 10 mm/mV settings. The fQRS was defined as the presence of various RSR' patterns, which included an additional R wave (R') or notching of the R or S wave in the presence of fragmentation (more than one R') in two contiguous leads corresponding to a major coronary artery territory.[5] The fQRS in wide QRS complex (≥ 120 ms) was included and defined as the QRS complex with >2 R' waves or notches in the R or S wave in a wide QRS complex of bundle branch block, or paced QRS, or premature ventricular complexes (PVC) in 2 contiguous leads.[9] Incomplete RBBB were excluded in this study.

The presence of fQRS was detected with the naked eye and analyzed by three independent observers blinded to angiography and clinical data. The inter-observer variability between observer 1 and observer 2 was 94.1% (k = 0.859) and between observer 1 and observer 3 was 91.2% (k = 0.810).

Coronary Angiography

Angiographic data of the patients were obtained from the catheter laboratory in the Cipto Mangunkusumo records and evaluated using this data. Complexity of coronary lesion was assessed by the degree of stenosis, by the number of vessels involved, and by a severity score, using Gensini score. Significant stenosis was defined as the diameter of stenosis calculated as ≥ 50% with quantitative angiography. If more than one vessel was involved, it was defined as multivessel stenosis.[10]

Gensini score were used to define the angiographic complexity of the coronary atherosclerotic lesion. The Gensini score is the sum of all segment scores. The severity numbers reflecting the specific percentage luminal diameter stenosis of the epicardial coronary arteries are 1 for 1–25% stenosis, 2 for 26–50% stenosis, 4 for 51–75% stenosis, 8 for 76–90% stenosis, 16 for 91–99% stenosis, and 32 for 100% stenosis. These numbers are multiplied by a constant number determined according to the territory of the coronary arteries. The Gensini scoring system is divided into three degree categories, i.e., mild for score <25, moderate for score 25–53, and severe for score > 53.[3]

Statistical Analysis

Statistical analysis in this study were carried out with SPSS for Windows (version 24.0, SPSS, Chicago, Illinois, USA). All quantitative variables were evaluated with the Kolgomorov-Smirnov test for normality. Quantitative variables were expressed as mean value with standard deviation (normal distribution data) or as median with interquartile range (non-normal distribution). Qualitative variables were expressed as percentages. Bivariate analysis was performed using an agreement test (kappa test) and a chi-square test or Fisher's exact test. A r value of more than 0.6 was considered good relationship, and a p value < 0.05 was considered statistically significant.

RESULTS

Of the 232 patients who underwent coronary angiography from the catheter laboratorium registry at Cipto Mangunkusumo from January to June 2018, 60 subject were excluded from our analysis because of pathological Q wave (n = 40), normal angiography in fQRS lead (n = 10), incomplete bundle branch block (n = 4), lack of ECG data (n = 2), and bad quality of ECG (n = 4). The data for final study of 172 subjects were enrolled in this study. Examples of various morphologies of fQRS on the ECG are shown in **Figure 2**.

The study showed the presence of fQRS in 94 (56%) patients. Fragmented QRS complexes was higher in male patients, elderly patients (age ≥ 60 years), diabetics, patients with hypertension, dyslipidemics, and smokers. In the study groups, the fQRS group was associated with the location of coronary lesion with higher incidence than the non-fQRS group. A baselines characteristic of the two groups (fQRS present versus absent) are shown in **Table 1**.

The group with fQRS demonstrated higher frequency of significant stenosis, multivessel disease, and high Gensini score compared to the non-fQRS group (**Table 2**). Bivariate analysis showed that fQRS was significantly positively associated with significant stenosis (kappa = 0.670), multivessel disease (kappa = 0.787), and high Gensini score (kappa = 0.820) (**Table 3**).

DISCUSSION

The study found that there was a higher frequency of fQRS among elderly, males, diabetics, hypertensions, dyslipidemics, and smokers with CAD. This finding was in agreement with Das et al. (2006), Sen et al. (2014), Bekler et al. (2015), and Rahman et al. (2016).[5, 11-13] All these are traditional risk factors for coronary atherosclerosis. These risk factors can trigger and aggravate the process of atherosclerosis, which causes the formation of lipid plaques resulting in coronary lesions. The process of progression of atherosclerosis in vascular causes perfusion changes, causing ischemic and myocardial infarction, which can be characterized by fQRS formation in ECG.[14-16]

In our study, fQRS had a significantly higher frequency among patient with severe degree of complexity coronary lesion. Patients with fQRS had significantly higher Gensini score, both consistent between numeric score and category group, in patients with CAD. Bivariate analysis

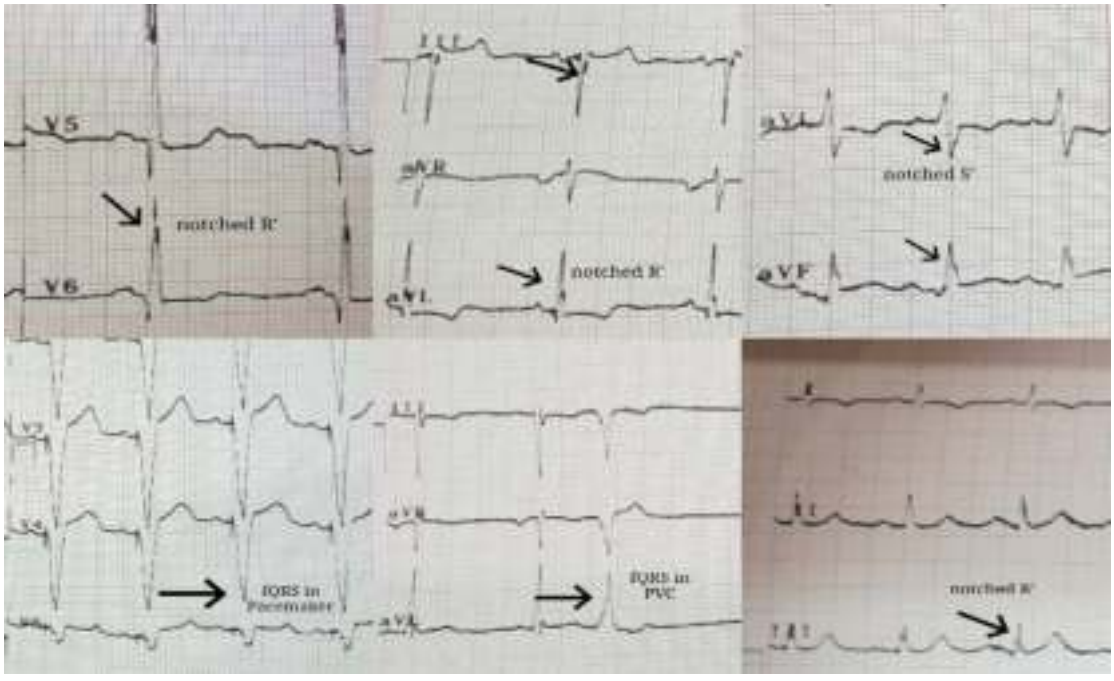

Figure 2. The various types of fragmented QRS complexes (fQRS) used for the study.

Table 1. Baseline characteristics of the study population.

Characteristics	Total N = 172	fQRS group (n%) n = 94 (54.6%)	Non-fQRS group (n%) n = 78 (45.3%)
Gender, n (%)			
Male	124	75 (60.5)	49 (39.5)
Female	48	19 (39.6)	29 (60.4)
Age (years)			
Mean, (SD)		59 (9.9)	58 (9.7)
Age category, n (%)			
< 60 years	94	48 (51.1)	46 (48.9)
≥ 60 years	78	46 (59.0)	32 (41.0)
Risk Factor			
Diabetic, n (%)			
Yes	79	49 (62.0)	30 (38.0)
No	93	48 (48.4)	57 (51.6)
Hypertension, n (%)			
Yes	120	63 (52.5)	57 (47.5)
No	52	31 (59.6)	21 (40.4)
Dyslipidemia, n (%)			
Yes	93	63 (67.7)	30 (32.3)
No	79	31 (39.2)	48 (60.8)
Smoker, n (%)			
Yes	94	66 (70.2)	28 (29.8)
No	78	28 (35.9)	50 (64.1)
Coronary Lesion			
LAD, n (%)	126	77 (61.1)	49 (38.9)
LCx, n (%)	92	48 (52.2)	44 (47.8)
RCA, n (%)	94	84 (89.4)	10 (10.6)

fQRS = fragmented QRS complexes; SD = Standard deviation; DM = Diabetes Mellitus; LAD = Left Anterior Ascending artery; LCx = Left Circumflex artery; RCA = Right Coronary Artery

Table 2. Comparison of coronary lesion complexity between fQRS and non-fQRS

	fQRS group (n%) n = 94 (546%)	Non-fQRS group (n%) n = 78 (45.3%)	P
Gensini Score			
Median, IQR*	85 (55.3)	8 (29.8)	< 0.001
*Non normal distribution			
Degree of complexity (Gensini)			
Mild, n (%)	4 (6.7)	56 (93.3)	< 0.001
Moderate, n (%)	13 (50.0)	13 (50.0)	
Severe, n (%)	77 (89.5)	9 (10.5)	
Degree of stenosis			
Non-significant (< 50%)	2 (7.1)	26 (92.9)	< 0.001
Significant (≥ 50%)	92 (63.9)	52 (36.1)	
Number of involved vessels			
Single	8 (21.1)	30 (78.9)	< 0.001
Multi	84 (80.8)	22 (19.2)	

IQR = Interquartile range; fQRS = fragmented QRS complexes

in this study showed that fQRS was significantly positively associated with complexity and severity of coronary lesion. Thus, the presence fQRS could predict and identify the complexity of coronary lesions.

This result may not only be due to an increase in the scar tissue but also jeopardized ischemic myocardium, which may in turn also contribute to non-homogenous conduction in the myocardium.[17] Das et al.[5] showed that the presence of an fQRS could detect the presence of a regional myocardial scar. Myocardial ischemia

can also alter the conduction causing the presence of fQRS, which showed the phenomenon formation of fQRS due to "electrical death" compared to "cells death". The concepts of myocardial stunning and hibernation may explain this phenomenon. At the cellular level, depletion of energy due to ischemia can cause critical stenosis. This process causes a conduction disturbance in the electrical homogeneity that can be expressed by fQRS formation on the ECG.[17]

The increase of infarct and ischemic area may be due to an increase in critical stenosis in more complex or severe coronary lesion. El-Dosouky et al. showed that fQRS could detect coronary stenosis in accordance with vascular territories.[7]

Study Limitations

There are several limitations in our study. This was a single-center study. It was nonrandomized, but we were careful to include subjects according to our inclusion and exclusion criteria. A second limitation is the relatively small sample size, but the sample size met the minimum requirement.

CONCLUSION

This study found a significant relationship between fQRS and the degree of severity of coronary lesion in CAD patients. The presence of fQRS, both narrow and wide, was associated with a higher degree of complexity of coronary lesions. We suggest that fQRS can be used as a predictive tool in identifying the complexity of coronary lesions and stratifying high risk CAD patients.

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CONFLICT OF INTEREST

There is no conflict of interest.

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Risk Factors for Temporary Vascular Access Infection in Patients with End-Stage Renal Disease Undergoing Hemodialysis in Cipto Mangunkusumo Hospital

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ABSTRACT

Background: *Temporary vascular access is used to provide adequate hemodialysis for patients who are initiating dialysis or are awaiting maturation of a more permanent vascular access. However, infection is one of the most frequent complications of using temporary vascular access and is the second leading cause of death in patients undergoing hemodialysis after cardiovascular events. There has been no research on the risk factors for the incidence of infection in patients using temporary vascular access in Indonesia.* ***Methods:*** *This is a retrospective cohort study utilizing secondary data from medical records of 318 subjects aged 18 years and older with end-stage renal disease and undergoing hemodialysis using temporary vascular access at Cipto Mangunkusumo Hospital.* ***Results:*** *Temporary vascular access infection was found in 125 of 318 subjects (39.3%). The risk factors of temporary vascular catheter infection in the multivariate analysis were females (OR 1.731; 95% CI 1.050-2.854; p=0.032), low hemoglobin levels (OR 2.293; 95% CI 1.353-3.885; p=0.002), presence of diabetes mellitus (OR 2.962; 95% CI 1.704-5.149; p<0.001) and duration of catheter insertion (OR 5.322; 95% CI 1.871-15-135; p=0.002). The association between ferritin and catheter insertion site was not analyzed as a risk factor because it was not performed in all subjects.* ***Conclusion:*** *The incidence of infection in patients with end -stage renal disease undergoing hemodialysis using temporary vascular access at Cipto Mangunkusumo Hospital was 39.3%. Female gender, low hemoglobin level, diabetes mellitus, and duration of catheter insertion were risk factors for temporary vascular access infection.*

Keywords: *Risk factors, temporary vascular access infection, end-stage renal disease, chronic kidney disease, hemodialysis.*

INTRODUCTION

Chronic kidney disease (CKD) is a complex condition characterized by decreased kidney function. Patients diagnosed with CKD can survive with the help of renal replacement therapy, one of which is dialysis. Based on the 2016 NKF-KDOQI guidelines regarding CKD, the recommended management for CKD patients includes dialysis through vascular access for hemodialysis. The usage number of hemodialysis catheters as vascular access increases linearly coinciding with the increase in new hemodialysis patients.[1]

A common complication that can occur after installing hemodialysis access is infection. Three factors known to influence the occurrence of bacteremia in hemodialysis patients are patient immunity, bacterial virulence, and hemodialysis procedures. Infections after hemodialysis catheter insertion can cause various complications such as local infection at the exit-site to hemodynamic instability, changes in mental status, and death. Patients undergoing hemodialysis through temporary access have a 2-3 times greater risk of infection and death than those using permanent access.[2]

To date, there have been no studies in Indonesia that explored the risk factors predisposing patients to infection after temporary vascular access placement. By understanding the risk factors associated with infection after hemodialysis catheter insertion, further actions can be undertaken to control the source of infection to reduce the percentage of post-catheter insertion infections in hemodialysis patients.

METHODS

A retrospective analysis was conducted on CKD patients undergoing hemodialysis in Cipto Mangunkusumo Hospital, Jakarta, Indonesia from January 2015 until the required sample size was met. The inclusion criteria for the study were adult CKD patients (aged ≥ 18 years) who underwent hemodialysis with temporary vascular access, either in the femoral, internal jugular, or subclavian vein, and presented with infection. Patients with an infection prior to being diagnosed with an infection related to the insertion of a temporary catheter or infection outside the catheter insertion site, patients with missing data in the medical record, and patients using immunosuppressive drugs or were under medications that decreased the immune system, were excluded from the study.

The data retrieved include patient characteristics such as age, gender, hemoglobin level, albumin level, duration of catheter use, presence of diabetes mellitus, hypertension, heart failure and malignancy, catheter insertion location, culture results, and antibiotics used to treat the infection. The outcome of this study was the incidence of temporary vascular access infection.

Ethical Clearance

The ethical clearance was issued by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital, with approval number KET-1227/UN2.F1/ETIK/PPM.00.02/2020.

Statistical Analysis

The statistical analyses were done electronically using the SPSS software. Data regarding the baseline clinical characteristics of research subjects were presented in tables. Categorical data were presented in percentages. Bivariate analysis was performed using the Chi-square test for nominal variables. In the bivariate analysis of nominal variables, if the Chi-square test conditions were not satisfied, Fisher's exact test or Kolmogorov-Smirnov test was used instead. All the bivariate outcome variables with a $p<0.25$ were included in the multivariate analysis using logistic regression.

RESULTS

From 2607 patients with CKD in need of hemodialysis found in the hospital database, a total of 318 patients were included in this study. The reason for the exclusion of the subjects were patients with an infection before being diagnosed with an infection related to the insertion of a temporary catheter or infection outside the catheter insertion site, incomplete or missing data of patients in the medical record, and patients using immunosuppressive drugs **(Figure 1).**

The characteristics of the included and excluded subjects undergoing hemodialysis with

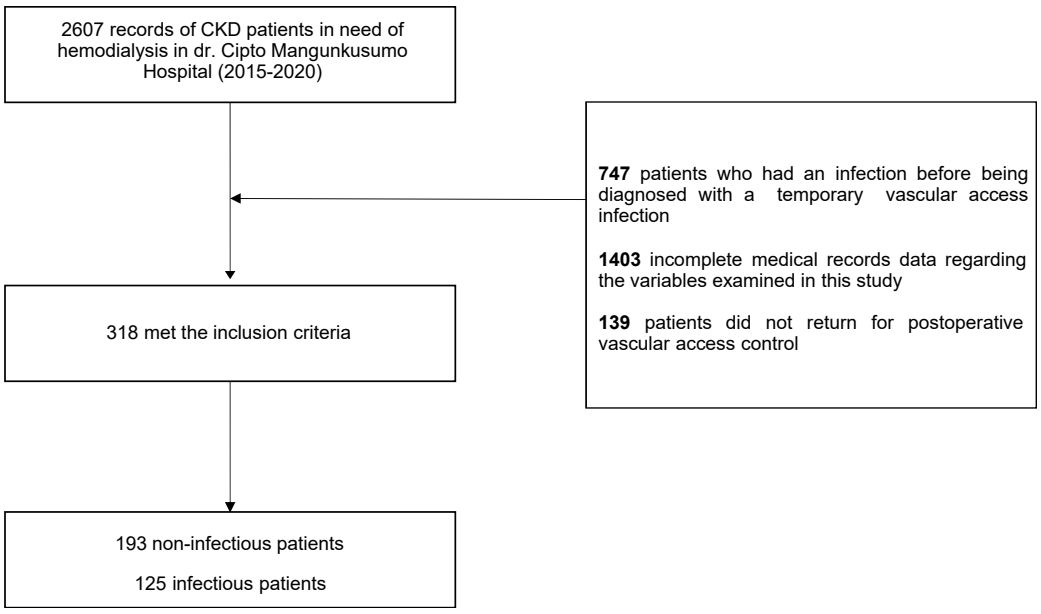

Figure 1. Flow diagram showing the patient selection.

temporary non-tunneled vascular access were not significantly different **(Table 1).** Overall, the included subjects had a mean age of 51.7 years, 160 were males, and 158 were females. The CKD patients with infection had a median age of 54 years (IQR 41-46 years), while those not infected had a median age of 55 years (IQR 46-63 years). Comorbid conditions such as hypoalbuminemia

Table 1. Characteristic comparison of the included and excluded groups.

Variables	Data	
	Included (318)	**Excluded (2289)**
Age (years), Median (IQR)	55 (43-62)	53 (42-61)
Age, n (%)		
≥ 60 years	92 (28,9)	602 (26,4)
< 60 years	22 (71,1)	1682 (73,6)
Gender, n (%)		
Male	160 (50,3)	1155 (50,7)
Female	158 (49,7)	1125 (49,3)
Hemoglobin level, n (%)		
< 10 g/dL	102 (32,1)	965 (44,2)
≥ 10 g/dL	216 (67,9)	1217 (55,8)
Albumin, n (%)		
Hypoalbuminemia (< 3.50 mg/dL)	193 (64,8)	858 (68,0)
Normoalbuminemia (≥ 3.50 mg/dL)	105 (35,2)	403 (32,0)
Ferritin, n (%)		
Low Risk infection (< 3822 µg/L)	108 (100,0)	689 (100,0)
High Risk Infection (≥ 3822 µg/L)	0 (0,0)	0 (0,0)
Duration of catheter use, n (%)		
≥ 30 days	83 (26,3)	364 (26,0)
< 30 days	233 (73,7)	1034 (74,0)
Urea, Median (IQR)	162,5 (111,63-213)	141,8 (105,4-183,0)
Creatinine, Median (IQR)	7,89 (5,56-10,90)	7,10 (4,9-10,90)
eGFR, Median (IQR)	7,85 (5,02-13,0)	8,4 (5,85-11,10)

were found in 64.8% of subjects, followed by diabetes (64.8%), hypertension (64.2%), anemia (31.8%), heart failure (10.1%), and malignancy (7.9%) **(Table 2)**. Vascular access was installed in the femoral vein in 57.9% of subjects, the jugular vein in 40.5% of subjects, and the subclavian vein in only 1.6% of subjects. Evaluation of ferritin, procalcitonin (PCT), and lactate levels was only performed in patients with infection, so they were not used as comparisons. Ferritin levels <1000 ug/L were found in 108 infected subjects, and procalcitonin levels >1.5 were found in 24 infected subjects. In addition, lactate levels >2 were found in 102 infected subjects.

Culture examinations were not performed on 130 subjects. Of the 188 subjects who had undergone culture examination, 61 samples did not show any bacterial growth, which could be due to the improper sampling technique and the timing of sampling, which could only be done after the subjects had received antibiotics. Furthermore, the most widely used antibiotics to treat transient vascular access infections were cefixime (53.2%), meropenem (10.6%), cefepime (6.4%), levofloxacin (6.4%), and ceftriaxone (6.4%). Based on the bivariate analysis, age was

Table 2. Clinical characteristics of research subjects.

Variables	Total
Age (years), Median (IQR)	
Age, n (%)	
≥ 60 years	101 (31.8)
< 60 years	217 (68.2)
Gender, n (%)	
Male	160 (50.3)
Female	158 (49.7)
Hemoglobin level, n (%)	
< 10 g/dL	101 (31.8)
≥ 10 g/dL	217 (68.2)
Albumin, n (%)	
Hypoalbuminemia (< 3.50 mg/dL)	193 (64.8)
Normoalbuminemia (≥ 3.50 mg/dL)	105 (35.2)
Random plasma glucose, n (%)	
DM (≥ 200 mg/dL)	206 (64.8)
Non-DM (< 200 mg/dL)	112 (35.2)
Duration of catheter use, n (%)	
≥ 30 days	21 (6.6)
< 30 days	295 (93.4)
Hypertension, n (%)	
Yes	204 (64.2)
No	114 (35.8)
Heart failure, n (%)	
Yes	32 (10.1)
No	286 (89.9)
Malignancy, n (%)	
Yes	25 (7.9)
No	292 (92.1)
Location of catheter use, n (%)	
Femoral vein	183 (57.9)
Jugular vein	128 (40.5)
Subclavian vein	5 (1.6)
Urea, Median (IQR)	162.5 (111.63-213)
Creatininea, Median (IQR)	7.89 (5.56-10.9)
Blood culture	
No bacterial growth was found	61 (31.9)
Not done	130 (68.1)

not a risk factor for infection (RR 0.938, 95%CI 0.696-1.266, p=0.675) **(Table 3)**.

DISCUSSION

Despite the benefits of providing adequate hemodialysis for patients initiating dialysis or awaiting permanent access, temporary vascular access has a higher risk of infection. Temporary vascular access infection is the second leading cause of mortality after cardiovascular events.[3] The incidence of catheter-related bloodstream infection ranges between 0.6 and 6.5 episodes per 1000 catheter days.[4] The pathogens use two main routes to reach the bloodstream: the extraluminal and intraluminal pathways. Regardless of the route used, after entering the bloodstream, the organisms can attach directly to the surface of the vascular access or become incorporated in the fibrin sheath that envelops the catheter and usually forms within 24 hours of catheter insertion. Adherence of organisms to the surface of the catheter initiates the formation of biofilms that are highly resistant to antibiotics. Therefore, it is clear that the most critical step in the treatment of catheter-related bloodstream infection (CRBSI) is preventing the attachment of microorganisms to the catheter and the formation of a biofilm. The first preventive step is to identify risk factors for infection, including gender, anemia, diabetes mellitus, duration of catheter use, old age, ferritin, hypoalbuminemia, and catheter insertion location.[4,5]

Several studies have shown that men have higher risks than women for developing catheter-related infections. Borges PRR et al showed that 65% of subjects with infection were males.[6] This was different from the results obtained from our study, where females had more infections (57.6%; OR 1.731; 95%CI 1.050-2.854; p=0.032) **(Table 4)**. This could happen since most of the female subjects in our study had more comorbidities and worse general condition when they first initiated hemodialysis.

Anemia is common in patients with chronic renal failure due to the shortened life span of red blood cells caused by hemolysis, folic acid deficiency, and bone marrow suppression by excess uremic substances, which further

Table 3. The comparison between independent variables with the proportion of temporary vascular access infection.

Variables	Infection		RR (95% CI)	p
	Yes	No		
Age, n (%)				
≥ 60 years	38 (37.6)	63 (62.4)	0.938 (0.696-1.266)	0.675
< 60 years	87 (40.1)	130 (59.9)		
Gender, n (%)				
Female	72 (45.6)	86 (54.4)	1.376 (1.041-1.817)	**0.023**
Male	53 (33.1)	107 (66.9)		
Anemia, n (%)				
Yes	53 (52.5)	48 (47.5)	1.582 (1.214-2.061)	**0.001**
No	72 (33.2)	145 (66.8)		
Hypoalbuminemia, n (%)				
Yes	87 (45.1)	106 (54.9)	1.246 (0.925-1.678)	0.138
No	38 (36.2)	67 (63.8)		
Diabetes Mellitus, n (%)				
Yes	95 (46.1)	111 (53.9)	1.722 (1.226-2.419)	**0.001**
No	30 (26.8)	82 (73.2)		
Duration of catheter use, n (%)				
≥ 30 days	15 (71.4)	6 (28.6)	1.951 (1.432-2.358)	**0.002**
< 30 days	108 (36.6)	187 (63.4)		
Location of catheter use, n (%)				
Femoral vein	72 (39.3)	111 (60.7)	4.728 (0.331-67.589)	0.252
Jugular vein	53 (41.4)	75 (58.6)	4.977 (0.347-71.274)	0.257
Subclavian vein	0 (0,.0)	5 (100.0)	Comparator	

Table 4. Multivariate analysis

Variables	OR (95% CI)	p
Gender: female	1.731 (1.050-2.854)	0.032
Anemia	2.293 (1.353-3.885)	0.002
Diabetes mellitus	2.962 (1.704-5.149)	<0.001
Duration of catheter use ≥ 30 days	5.322 (1.871-15.135)	0.002

causes failure of erythropoietin production and decreased red blood cell production. Additionally, iron deficiency is known to play a role in causing anemia in chronic renal failure patients. Iron is an essential element in the immune process. Iron deficiency can cause impaired phagocyte function and increase the risk of infection and death from infection.[7] Based on the results of a study by Wang K et al. involving 865 subjects, low hemoglobin levels were a significant risk factor for the incidence of infection (OR 2,276; 95%CI 1,0101-4,749; p=0.012) [8]. These results support the findings in our study where infection occurred in 52.5% of subjects who had anemia and 33.2% in subjects who did not have anemia (OR 2.293; 95%CI 1.353-3.885; p=0.002).

Diabetes causes immune system disorders, including decreased humoral and cellular immunity, which play a role in the pathogenesis of CRBSI. Diabetes causes decreased mobility of polymorphonuclear cells, chemotactic and phagocytic functions, and impaired adherence function, also decreased the number of T lymphocytes, especially CD4, which decreases the CD4:CD8 ratio. Grothe et al showed that diabetic patients in hypertonic conditions had a 22% greater chance of catheter infections. Menegueti et al reported the result of a case-control study indicating that diabetes mellitus was a risk factor for catheter infection (OR 2.651; p<0.001). Another study by Sahli et al. also proved that diabetes significantly increases a person's risk of CRBSI.[4,8,9] Similarly, a retrospective cohort study by Çaylan R et al. found that diabetes mellitus was associated with infection (OR 2.20; 95%CI 1-4.82; p=0.049).[10] This was in line with the results obtained from this study; 76% of the infected subjects were diabetic (OR 2.962; 95%CI 1.704-5.149; p<0.001).

Generally, the recommended duration of catheter use is <21 days, but the 30-day limit was used in this study.[11] Napalkov et al. reported that most temporary vascular access infections occurred within the first 90 days, with an incidence rate of 5.1 per 1000 catheter days. The risk of infection was also higher as the duration of use increased, going up to 3.3 times in a period >90 days.[8] Meanwhile, Borges PRR et al. found that an average catheter infection occurred after 9 days of use.[6] These results were supported by Oliver MJ et al.[12] through his research which showed the possibility of bacteremia on the first day of catheter insertion was 1.9% and significantly increased to 13.4% on the second day. This indicated an association between the increased risk of CRBSI and the duration of catheter use. Similar results were obtained from our study, where there were 71.4% of subjects using catheters >30 days developing an infection (OR 5.322; 95%CI 1.871-15.135; p<0.002), compared to 63.4% of patients using catheter <30 days who did not have an infection.

There are changes in non-specific systems that happen due to aging that facilitates the invasion of pathogenic organisms into the mucosal tissue. Increase in the plasma concentration of IL-6, IL-1, and tumor necrosis factor-alpha (TNF-α) in the elderly was also shown to be a predictor of functional disability and mortality and causes continuous stimulation of the immune system, resulting in a subclinical inflammatory state or what is known as inflamm-aging. The aging process also impacts the specific immune system, causing a decrease in the number of T and B lymphocytes.[13]

Our analysis showed no statistically significant correlation between age >60 years and infection. This could be because the mean age in all groups with temporary vascular access was 51.7 years, and 68.2% of the infectious subjects were aged <60 years old. Similar results were

found by the study of Borges PRR et al where age was not a significant risk factor for infection.[6]

Ferritin indicates the amount of iron stored in the body. A high ferritin level in the serum shows high iron content in the body. CKD patients undergoing dialysis therapy generally have iron overload caused by the body's increased need for red blood cells, so they need to be given iron intravenously, with or without red blood cell transfusions. Simultaneously, excess iron can cause damage to neutrophils and T cell function. Ferritin protects the body during infection by limiting the availability of iron used by pathogens for multiplication and colony formation.

A study by Seifert et al showed an increased incidence of bacterial infection in hemodialysis patients with ferritin levels ranging from 1001-2000 ng/mL compared to patients with serum ferritin levels ranging from 10-220 ng/mL ($p<0.01$).[7] Another prospective study reported a 2.92 times greater risk in patients undergoing hemodialysis with ferritin levels >1000 ng/mL than those with ferritin levels <1000 ng/mL.[14] The relationship between ferritin levels and the risk of infection in this study could not be analyzed further because a ferritin examination was not performed on every subject undergoing hemodialysis.

Hypoalbuminemia is common in patients undergoing dialysis. Inadequate nutrition is associated with impaired immunity, increasing the likelihood of becoming infected.[15] Lukowsky et al reported that one-third of deaths within the first 90 days in patients undergoing hemodialysis was associated with hypoalbuminemia. The multivariate analysis emphasized that albumin levels <33 g/dL were an independent predictor of catheter infection. A case-control study conducted by Adeniyi OA, et al.[16] found that serum albumin levels before treatment in subjects with vascular access infection were in the range of 2.4 ± 0.6 g/dL, while for the group of subjects who did not have an infection, had an albumin value of 3.2 ± 0.6 g/dL ($p<0.0001$). Another study by Darma et al also showed an increased risk of catheter-associated bacteremia in patients with hypoalbuminemia ($p<0.008$).[17,18] In addition, similar findings were also shown by Demirci et al,[3] where low albumin levels were an independent predictor of the occurrence of CRBSI (OR 0.119, 95% CI 0.019-0.756, $p=0.024$).[15] Our study was consistent with the results, where 69.6% of subjects with hypoalbuminemia had an infection, while only 30.4% of subjects were infected in the group with a normal albumin level.

The location of catheter insertion could also impact the incidence of infection. Insertion of temporary CVC to the femoral vein is associated with a higher risk of infection. Sahli et al reported that the incidence of infection in CVC installed in the femoral vein is 8.8 per 1000 catheter days. Meanwhile, the subclavian vein has the lowest risk of infection, despite a higher risk of stenosis. Thus, the internal jugular vein is preferred for hemodialysis.[4,19] This risk of stenosis was also the exact reason for not preferring the subclavian vein as a CVC insertion site at Cipto Mangunkusumo Hospital; hence the correlation between the catheter insertion location and the risk of infection in our study could not be analyzed further.

KDOQI recommended that health workers who come into contact with catheters must use clean or sterile masks and gloves. Liquids that can be used to clean the exit sites are 2% chlorhexidine and 70% alcohol or 10% povidone-iodine liquid. Several studies and meta-analyses have shown that chlorhexidine is superior to alcohol and povidone-iodine. Technical implementation of exit-site maintenance at Cipto Mangunkusumo Hospital has also used 2% chlorhexidine.[5]

The use of topical antibiotics at the exit site has been associated with a 75-93% reduced risk of CVC-associated bacteremia. One of the recommended topical antibiotics, which are used in Cipto Mangunkusumo Hospital, is mupirocin. In addition, antimicrobial lock prophylaxis has been shown to reduce the risk of CVC-related bacteremia. Antimicrobial lock combination prophylaxis, which is currently being used at Cipto Mangunkusumo Hospital, is gentamicin 40 mg and heparin 2000 units. This use was in line with the International Society of Nephrology recommendations: gentamicin 5 mg/ml + heparin 5000 U/mL. Overall, this could

cause a low incidence of CVC infection in Cipto Mangunkusumo Hospital.[5]

Our study has several limitations. First, this study was a retrospective study that relied on medical record data; thus, it may not fully reflect the patient's condition if there were improper or incomplete documentation in the medical record. Second, data collection was only done in one hospital; therefore, the results obtained may not represent the results from other hospitals. Third, we did not assess the comorbid factors of each subject before temporary vascular access insertion, which could inherently affect the patient's susceptibility to infection.

CONCLUSION

The proportion of temporary vascular access infections at the Cipto Mangunkusumo Hospital was 39.3%. The significant risk factors for temporary vascular access infection were female gender, diabetes mellitus, low hemoglobin level, and the duration of catheter use >30 days. We recommend that ferritin examination be performed routinely in all patients with temporary vascular access, regardless of the infection status. Blood cultures should be examined twice, with samples from peripheral veins and hemodialysis catheters taken before administration of antimicrobial therapy and observed for 48 hours of incubation. Culture studies should be performed after excluding other possible infection causes in patients with fever. More research should be carried out, preferably using a prospective design, to assess the actual condition of the patient better and to be able to follow the patient's course of disease continuously. Lastly, further research should pay more attention to the characteristics and proportions of each of the subjects involved to show more accurate results and reduce the possibility of bias.

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The Association Between Uric Acid and Symmetric Dimethylarginine Levels in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis

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ABSTRACT

***Background**: Uric acid (UA) levels are associated with increased risk of cardiovascular events and mortality in hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients. In a study with a population of healthy young adults and HD there was a correlation between high blood uric acid levels and blood symmetric dimethylarginine (SDMA) level. However, in CAPD population, there are still conflicting data on the mechanism of increased risks related to uric acid levels. This study aimed to assess the association between uric acid levels and SDMA in the subjects undergoing CAPD.* **Methods:** *This was a cross – sectional study conducted in all the adults who underwent CAPD for at least three months in tertiary hospital in Jakarta, Indonesia. Subjects already on uric lowering therapy, pregnant or lactating women, and those with a history of malignancy were excluded. Uric acid and SDMA level were measured at the same time patients controlled to outpatient clinic. Bivariate analysis was performed using the Mann – Whitney test and multivariate analysis performed using logistic regression test.* **Results:** *A total of 55 subjects were included. The median level of UA was 7.30 $\pm$ 1.59 mg/dl and 33 subjects (60%) had UA levels of 7 mg/dl or higher. The median SDMA level was 633.73 $\pm$ 231.54 ng/mL. Subjects with UA levels > 7 mg/dl had significantly higher SDMA levels compared to subjects with UA levels $\leq$ 7 mg/dl (721.58 $\pm$ 220.57 vs 501.95 $\pm$ 182; P < 0.001). The cut – off value of SDMA 536 ng/mL was obtained from the receiver operating characteristic (ROC) curve with sensitivity 81.8%, specificity 63.6%, PPV 77.78% and NPV 73.68%. After fully adjusted with the confounders, the determinant factors in this study were diabetes mellitus (OR: 7.844; CI95%: 1.899 – 32.395: P value: 0.004) and dyslipidemia (OR: 6.440; CI95%: 1.483 – 27.970; P value: 0.013) as risk factors.* **Conclusion**: *In CAPD patients, UA levels above 7 mg/dl were associated with increased SDMA levels. This study demonstrates the determinant factors regarding association between UA level and SDMA in CAPD patients were diabetes mellitus and dyslipidemia. The cut – off value of SDMA above 536 ng/mL were significant to increased risk of cardiovascular events.*

***Keywords**: uric acid, SDMA, CAPD.*

INTRODUCTION

Peritoneal dialysis (PD) is not very popular as a treatment choice for end stage renal disease (ESRD) patients in Indonesia. The prevalence was only 2% in 2018 and continuous ambulatory peritoneal dialysis (CAPD) is the only type of PD system available in Indonesia.[1] The prevalence of cardiovascular disease (CVD) in ESRD patients on dialysis was 50% and it was 20 times higher than in the general population.[2] The cause of death from cardiovascular disease in dialysis patients is multifactorial.[2,3]

Hyperuricemia is known to be associated with increased oxidative stress, inflammation, and endothelial dysfunction by inhibiting nitric oxide function. A study reported that hyperuricemia increased the risk of all – cause and cardiovascular disease related mortality in CKD especially in hemodialysis (HD) patients.[4] However, despite hyperuricemia being suggested as a risk factor in HD population, there are still controversies in PD population. Uric acid (UA) levels in HD population presents in J – shape trends whereas PD population present in U – shape trends of mortality.[5,6]

In addition to uric acid (UA), some uremic toxins, including symmetric dimethylarginine (SDMA), were shown to be associated with cardiovascular disease.[7] As a valuable and sensitive marker of renal function, SDMA is also an independent risk factor for cardiovascular disease and mortality.[5,7] Symmetric dimethylarginine (SDMA) showed a vital role in the inflammatory process and ROS generation. An in vitro study assessing ten guanidino compounds suggested SDMA as a compound with the most significant role in vascular damage and the secretion of proinflammatory mediators.[8] SDMA along with uric acid is the most potent endogenous inhibitor of nitric oxide synthase with higher levels in patients with end stage renal disease (ESRD). SDMA has been an outstanding marker of renal function both in human an in animal models, with ESRD patients on dialysis showing the highest SDMA levels.[7] Yassir et al had been demonstrated that there was a significant association between UA and SDMA levels in chronic twice – weekly HD.[9]

However, there is still a lack of understanding about the association between uric acid and SDMA levels in PD patients especially CAPD patients. This study aimed to assess the association between the levels of UA and SDMA in the subjects undergoing CAPD. Therefore, this study can be applied in future management of PD patients in order to prevent cardiovascular manifestations.

METHODS

This cross-sectional study was conducted in the CAPD outpatient unit of Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, from June to August 2021. We consecutively included all patients aged 18 years and older undergoing CAPD for at least three months in our hospital. The subjects who were already on uric acid lowering therapy, pregnant or lactating women, and patients with a history of malignancy were excluded.

History taking, physical examination, and blood tests were obtained. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m^2). Based on the WHO Asia Pacific classification, BMI cut-offs were regarded as the following: normal (18.5 - 22.9 kg/m^2), underweight (< 18.5 kg/m^2), overweight (23 - 24.9 kg/m^2), obese I (25 - 29.9 kg/m^2), and obese II (> 30 kg/m^2). The patient's smoking history, the duration of CAPD, and the presence of diabetes and hypertension were recorded from medical records. Blood pressure was measured using Omron HEM-7203 meter and categorized as < 140 mmHg, 140 - 160 mmHg, and > 160 mmHg.

Venous blood samples were collected from each subject and stored in EDTA-containing tubes. The biochemical workup included uric acid, SDMA (liquid chromatography (LC)-Tandem mass spectrometry (MS/MS). Based on the mean UA levels obtained from previous study by Chang W et all in 2018, UA level was categorized into > 7 mg/dl and ≤ 7 mg/dl.[5]

The collected data is then analyzed by using SPSS for Windows programs. The data was analyzed using an un – paired t – test. In addition, bivariate analysis was performed using the Mann – Whitney test and multivariate analysis performed using logistic regression test. P – Values of < 0.05 were considered statistically significant.

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia, approved the study with the approval number of KET-467 / UN2.F1 / ETIK / PPM.00.02 / 2021. All the participants included in this study gave informed consent freely and voluntarily. The participants were given an opportunity to ask their questions, to all of which we provided adequate responses. None of the participants were coerced to give consent.

RESULTS

Characteristics of Subjects present in **Table 1**. The study was conducted on patients who undergo CAPD in outpatient clinic of RSCM Jakarta, involving 55 people as the subject of the study. The participants mean age was 40.71 ± 14.39 years old (min: 18, max: 71) and males constituted 63.6% of the subjects. The median duration of CAPD was 27 months (min: 13, max: 42). The major cause of ESRD was glomerulonephritis (47.3%), diabetes mellitus (25.5%), and hypertension (25.5%). We found that the mean UA level was 7.30 ± 1.59 mg/dl and 33 subjects (60%) had UA level 7 mg/dl or higher. Meanwhile, the mean SDMA level in all 55 subjects was 633.73 ± 231.54 ng/mL.

Subjects with UA levels > 7 mg/dl had significantly higher SDMA levels compared to subjects with UA levels ≤ 7 mg/dl (721.58 ± 220.57 vs 501.95 ± 182; P < 0.001). (**Table 2**)

The cut – off value of SDMA 536 ng/mL was obtained from the receiver operating characteristic (ROC) curve with sensitivity 81.8%, specificity 63.6%, PPV 77.78% and NPV 73.68%. After fully adjusted with the confounders, the determinant factors in this study were diabetes mellitus (OR: 7.844; CI95%: 1.899 – 32.395: P value: 0.004) and dyslipidemia (OR:

Table 1. Demographic characteristics of study subjects.

Variables	N=55
Gender, n (%)	
□ Man	35 (63.6)
□ Women	20 (36.4)
Age (years), mean (SD)	40.71 (± 14.39)
Categorical of Age, n (%)	
□ ≤ 45 years	20 (36.4)
□ > 45 years	35 (63.6)

Table 1. Demographic characteristics of study subjects.

Variables	N=55
BMI (Kg/m^2), mean (SD)	23.17 (± 4.30)
Categorical of BMI, n (%)	
□ Normal	29 (52.7)
□ Underweight	10 (18.2)
□ Overweight	13 (23.6)
□ Obesity 1	3 (5.5)
□ Obesity 2	0 (0.0)
Hypertension, n (%)	
□ Yes	50 (90.9)
□ No	5 (9.1)
Diabetes mellitus, n (%)	
□ Yes	14 (25.5)
□ No	41 (74.5)
Dyslipidemia, n (%)	
□ Yes	29 (52.7)
□ No	26 (47.3)
Duration of CAPD, n (%)	
□ > 3 years	17 (30.9)
□ ≤ 3 years	38 (69.1)
Duration of CAPD (months), Median	27 (13-42)
Ureum (mg/dl), Median	97.6 (79.7-117.0)
Creatinin (mg/dl), mean (SD)	11.61 (± 4.71)
Hemoglobin (g/dl), mean (SD)	9.46 (± 1.58)
Anemia (Hb < 11 g/dl), n (%)	
□ Yes	45 (81.8)
□ No	10 (18.2)
Hypoalbuminemia (Albumin < 3.5 g/dl), n (%)	
□ Yes	24 (43.6)
□ No	31 (56.4)
The use of dialysate concentration glucose base 2.5% > 2x a day, n (%)	
□ Yes	21 (38.2)
□ No	34 (61.8)
History of Peritonitis, n (%)	
□ Yes	17 (30.9)
□ No	38 (69.1)
Membrane Type, n (%)	
□ High transporter	29 (52.7)
□ Low transporter	26 (47.3)
Cause of ESRD, n (%)	
□ Glomerulonephritis	26 (47.3)
□ Diabetes mellitus	14 (25.5)
□ Hypertension	14 (25.5)
□ Kidney Stone	0 (0.0)
□ ADPKD	1 (1.8)
SDMA, mean (SD)	633.73 ± 231.54
Uric Acid, mean (SD)	7.30 ± 1.59
Categorical of Uric Acid, n (%)	
□ > 7 mg/dl	33 (60.0)
□ ≤ 7 mg/dl	22 (40.0)

DM, diabetes melitus; BMI, body mass index; SD, standard deviation; *SDMA, Symmetric Dimethylarginine; ADPKD, Autosomal Dominan polycystic kidney disease.*

6.440; CI95%: 1.483 – 27.970; P value: 0.013) as risk factors. (**Table 3 – 5**)

Table 2. Uric Acid to SDMA level.

Variables	Uric Acid Category		P
	> 7 mg/dl	≤ 7 mg/dl	
SDMA	721.58 ± 220.57	501.95 ± 182	<0.001

DISCUSSION

This study shows a significant association between UA and SDMA levels in 55 subjects under CAPD. We found that elevated UA levels (> 7 mg/dl) were associated with higher SDMA levels compared to subjects with UA levels ≤ 7 mg/dl (721.58 ± 220.57 vs 501.95 ± 182; P < 0.001). Our study was the first to evaluate serum

Table 3. Cut – off SDMA based on ROC curve.

Variables	SDMA Level		PR (CI 95%)	p
	> 536 ng/mL	≤ 536 ng/mL		
Category Uric Acid				
> 7 mg/dl	28 (84.8)	5 (15.2)	2.333 (1.318-4.131)	<0.001
≤ 7 mg/dl	8 (36.4)	14 (63.6)		

Table 4. Confounding factors related to SDMA level.

Confounders	SDMA Level		P
	> 536 ng/mL	≤ 536 ng/mL	
Age, n (%)			
≤ 45 years	8 (40.0)	12 (60.0)	0.007
> 45 years	28 (80.0)	7 (20.0)	
Obesity, n (%)			
Yes	1 (33.3)	2 (66.7)	0.272
No	35 (67.3)	17 (32.7)	
Diabetes mellitus, n (%)			
Yes	6 (42.9)	8 (57.1)	0.054
No	30 (73.2)	11 (26.8)	
Hypertension, n (%)			
Yes	34 (68.0)	16 (32.0)	0.327
No	2 (40.0)	3 (60.0)	
Dyslipidemia, n (%)			
Yes	16 (55.2)	13 (44.8)	0.159
No	20 (76.9)	6 (23.1)	
Duration of CAPD, n (%)			
> 3 years	8 (47.1)	9 (52.9)	0.107
≤ 3 years	28 (73.7)	10 (26.3)	
Anemia, n (%)			
Yes	30 (66.7)	15 (33.3)	0.723
No	6 (60.0)	4 (40.0)	
Hypoalbuminemia, n (%)			
Yes	16 (66.7)	8 (33.3)	1.000
No	20 (64.5)	11 (35.5)	
The use of dialysate concentration glucose base 2.5% > 2x a day, n (%)			
Yes	12 (57.1)	9 (42.9)	0.467
No	24 (70.6)	10 (29.4)	
History of Peritonitis, n (%)			
Yes	9 (52.9)	8 (47.1)	0.318
No	27 (71.1)	11 (28.9)	
Membrane Type, n (%)			
High Transporter	19 (65.5)	10 (34.5)	1.000
Low Transporter	17 (65.4)	9 (34.6)	

Table 5. Multivariate analysis.

Variables	OR (CI 95%)	Delta OR	p
Crude OR: Uric Acid to SDMA	9.800 (2.702-35.546)		0.001
Adjusted OR:			
+ Age	7.788 (2.014-30.115)	**25.83%**	0.003
+ DM	7.844 (1.899-32.395)	7.13%	0.004
+ Duration of CAPD	6.747 (1.574-28.915)	**16.25%**	0.010
+ Dyslipidemia	6.440 (1.483-27.970)	4.76%	0.013

SDMA level and its association with serum UA level in subject under CAPD.

Yassir et al had demonstrated that there was a significant association between UA and SDMA levels in chronic twice – weekly HD.[9] Uric acid is a product of purine metabolism which mainly excreted by the kidneys.[9,10] Consequently, hyperuricemia is highly prevalent in CKD patients.[3,5,6,11] So, UA serum concentration depends on the rate of purine metabolism and the efficiency of its renal clearance, which is easily affected by dialysis.[5,6,10]

The clinical implications of hyperuricemia in CAPD patients are still controversial. Studies showed that elevated UA levels in CAPD revealed as U – Shaped rather than J – Shaped uric acid mortality.[5,11] Based on Chang et al and Dong et al Studies, hyperuricemia is a risk factor for all cause and cardiovascular mortality.[5,11] Uric acid may act as a potent pro – inflammatory cytokines which can lead to the generation of other uremic toxins such as SDMA.[7]

As an uremic toxin, SDMA is a naturally generated amino acid that is removed from the body by the kidneys (> 90%).[7] As a low molecular weight water soluble uremic toxin, SDMA is rapidly cleared during dialysis.[7] In our study, the mean SDMA level in all 55 subjects was 633.73 $\pm$ 231.54 ng/ml and cut – off value of SDMA 536 ng/mL was obtained from the receiver operating characteristic (ROC) curve with sensitivity 81.8%, specificity 63.6%, PPV 77.78% and NPV 73.68%. This findings were slightly lower than HD population based on reported by Yassir et al.[9]

SDMA plays an important role in CKD development and progression. An elevation in SDMA level activates pro – inflammatory cytokines and also activates reactive – oxygen species (ROS) which in turn promotes the creation of modified high – density lipoprotein (HDL), causing HDL dysfunction.[7,9] After fully adjusted with the confounders, the determinant factors in this study were diabetes mellitus (OR: 7.844; CI95%: 1.899 – 32.395: P value: 0.004) and dyslipidemia (OR: 6.440; CI95%: 1.483 – 27.970; P value: 0.013) as risk factors.

The limitation of this study is that due to the nature of the study design, we could not assess the temporal relationship. Not all confounders were evaluated in this study which might have attenuated the association between UA and SDMA levels. In this study, we also did nor evaluate cardiovascular outcomes. This study was a single center study with small sample size which makes still difficult to ascertain if there is a clear linkage between UA and SDMA in CAPD patients. Nutritional assessment is also not included in this study which plays a role in increasing human resources and uric acid levels.

This study can be applied in future management of PD patients in order to prevent cardiovascular manifestations. However, another study should be held with cohort prospective and RCT regarding SDMA levels associated with risk factors and SDMA levels associated with PD adequacy, respectively.

CONCLUSION

In CAPD patients, UA levels above 7 mg/dl were associated with increased SDMA levels. This study demonstrates the determinant factors regarding association between UA level and SDMA in CAPD patients were diabetes mellitus and dyslipidemia. The cut – off value of SDMA above 536 ng/mL were significantly associated with increased risk of cardiovascular events.

However, it remains a challenge to determine the role of UA in the metabolic pathway of SDMA. Referring to the study's limitations, the

therapeutic consequences of our findings remain unclear, and other cohort studies are needed to confirm such findings and assess the adverse outcomes of this phenomenon in CKD patients who undergoing dialysis.

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Factors Associated with Absolute Neutrophil Count Dynamics and Docetaxel-Adryamicin-Cyclophosphamide (TAC) Chemotherapy Induced Neutropenia During Extended Filgrastim Administration in Breast Cancer Patients

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ABSTRACT

Background: *Myelosuppressive effects of chemotherapy for breast cancer treatment may trigger chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN). Filgrastim has been widely used as prophylaxis against CIN and FN. However despite filgrastim administration, some study showed FN still occur and cause patient vulnerability to infection. This study aims to evaluate factors associated with Absolute Neutrophil Count (ANC) dynamics and Docetaxel-Adryamicin-Cyclophosphamide (TAC) CIN during extended filgrastim administration in breast cancer patients.* ***Methods:*** *Patients were selected among breast cancer in-patients who fulfilled the eligibility criteria. Patient characteristics data and ANC were collected. The entire patients received 5μg/kg/day filgrastim by subcutaneous injection 24 hours post-chemotherapy. ANC was monitored daily and filgrastim administration was stopped when ANC reached >10000/mm^3 or 14 days of administration. Kruskall-Wallis test and Spearman Correlation test was performed to analyze ANC dynamics and CIN-related factors.* ***Results:*** *This study included 42 breast cancer patients. Patient age median was 52 (31-70) years old. ANC nadir could be observed around 5-7 days after chemotherapy and FN occurred in two out of 38 grade 4 neutropenia patients (4.8%). Critical ANC lasted for 1 day, 2 days, and 3 days respectively in 9 (23.7%), 25 (65.8%) and 4 (10.5%) patients. There was no correlation between neutropenia and age. ANC slope and recovery duration did not show a significant difference. However, depth of nadir is inversely correlated with the duration of ANC recovery (>10000/mm^3) and the duration during the peak on the 2nd day until reaching nadir both with fair strength, $r = -0.489$ and $r = -0.438$ ($p < 0.05$), respectively. No sepsis incidence had manifested.* ***Conclusion:*** *CIN still occurred in breast cancer patient receiving filgrastim primary prophylaxis regardless of age and neutropenia severity. Nadir as the lowest point of ANC should be noted as a pivotal milestone for ANC slope and recovery evaluation.*

Keywords**:** *breast cancer, cancer, TAC chemotherapy, febrile neutropenia, filgrastim.*

INTRODUCTION

Breast cancer is one of the most prevalent cancers in women that have caught the attention of clinicians and researchers worldwide.[1] Chemotherapy remains an important part of the standard cancer treatment, aside from surgery and radiotherapy.[2] Chemotherapy generally acts by inducing the death and mitosis arrest of malignant cells[3]; however, it causes significant adverse effects that continue to be a point of concern in clinical settings. These adverse effects of chemotherapy hinder multiple components of cancer management that include affecting the patients' motivation to undergo chemotherapy. Chemotherapy-induced neutropenia (CIN) is one of the critical hematological adverse effects that contribute greatly to the morbidity and mortality of patients.[4]

CIN is defined as a decline of neutrophils in the blood circulation due to administration of myelosuppressive chemotherapeutic agents.[5] Docetaxel, doxorubicin, and cyclophosphamide (TAC) combination chemotherapy for breast cancer is one such myelosuppressive regimen, which results in 22%–25% CIN occurrence.[4] CIN incidence steadily increases the infection risk and treatment delay in patients with cancer.[6] Granulocyte colony-stimulating factor (G-CSF) or filgrastim is an available growth factor medicament applied to stimulate myeloid granulocyte proliferation.[7] The prophylactic use of filgrastim potentially reduces the risk of CIN, and thus, its complications, including sepsis.[7] However, despite prophylaxis, CIN and febrile neutropenia (FN) still occur,[8–10] leaving patients vulnerable to infections. The degree of infection risk is a considerable matter of concern in patient management, particularly in tropical countries like Indonesia.[11]

Filgrastim administration has been proven to improve neutropenia especially in patients receiving high-risk myelosuppressive chemotherapy. In previous study of patients with breast cancer in Indonesia that received TAC chemotherapy suggested that even with filgrastim administration, FN still occurred in 12 out of 61 patients.[8] Another study of malignant lymphoma patients who received cyclophosphamide, cytarabine, etoposide and dexamethasone ± rituximab (CHASE(R)) also showed 30 out of 54 patients still suffered from FN despite the administration of filgrastim.[12] Various optimization of filgrastim administration could be adjusted in several aspects including dose, administration timing, duration, and absolute neutrophil count (ANC) target for improving CIN and FN outcomes in terms of complication, morbidity, mortality, length of stay, and medical expenses.[4] Extended filgrastim administration combined with a higher ANC target recovery modification could potentially improve the outcome of therapy.

The guidelines of filgrastim administration differ for the administration length and the indication to start its administration.[6,7,13] This study aims to assess ANC dynamics and CIN-related factors during extended filgrastim administration on breast cancer patients receiving the TAC regimen chemotherapy to pinpoint important parameters that correlates with ANC recovery aiming for a better monitoring during patient care.

METHODS

This study was a cross-sectional study of extended filgrastim administration during first cycle of TAC chemotherapy receiving breast cancer patients.

Patients

The study has been approved by the Ethical Committee in Health Research, Dr. Soetomo General Hospital Surabaya, as stated on the ethical clearance document no. 107/Panke. KKE/II/2017. The patients for this study were selected from the inpatients undergoing TAC chemotherapy regimens for breast cancer, admitted from February 2017 to December 2018 in Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. The inclusion criteria of the patients were as follows: female, diagnosed with breast cancer, and older than 18 years. This study did not include patients with any record of previous chemotherapy or patients diagnosed with malignancies other than breast cancer. Patients with neutropenia before chemotherapy administration were also excluded.

Minimum sample count was determined based on sample size formula for correlation test[14] $N = \{(Z_\alpha+Z_\beta)/ 0.5 \times \ln [(1 + r)/(1 – r)]\}2 + 3$, where N is the minimum sample size, Z_α is the standard normal deviate for α (0.05), Z_β is the standard normal deviate for β (0.2), and r is the expected correlation coefficient (0.5). The minimum sample required from the calculation was 29. A total of 42 patients were included in this study. Before enrollment, all the patients had given their informed consent. All the patients were treated in a non-sterile room in Graha Amerta, Dr. Soetomo Teaching Hospital, Surabaya, Jawa Timur, Indonesia. All the patients received the taxane (docetaxel 75 mg/m^2), Adriamycin (doxorubicin 50 mg/m^2 IV), and cyclophosphamide (500 mg/m^2) combination chemotherapy regimen on day zero in the 1st cycle. Filgrastim (5 μg/kg) was administered daily by a single subcutaneous injection, starting from the first 24 hours after chemotherapy (day one) and repeated with intervals of exactly 24 hours until the last dose. During the study, ANC was monitored and recorded each day at exactly 24-hour intervals together with filgrastim administration, patient related data was extracted through anamnesis and medical record, and the patients were monitored daily for incidence of sepsis using the quick sepsis-related organ failure assessment (qSOFA) score as assessment of infections related to depleted ANC condition. Nadir ANC is defined as the lowest ANC value during monitoring, whereas critical ANC is defined as ANC ≤500/mm^3. Filgrastim administration was continued for 14 days or until ANC reached more than 10000/mm^3, and the number of days of filgrastim administration was recorded.

Statistical Analysis

ANC evaluation statistical analysis was performed by assessing total duration of ANC recovery (ANC ≥10000/mm^3) among the entire subject post-TAC chemotherapy and filgrastim administration through Kruskall-Wallis test for analyzing similarity of ANC recovery duration during filgrastim administration. Further correlation analysis among ANC slope (duration from 2nd day ANC peak until reaching nadir), ANC recovery (duration from nadir until reaching ANC ≥10000/mm^3), and depth of nadir was performed through pairwise spearman correlation analysis.

ANC parameter analysis towards age was performed by analyze highest grade of neutropenia, critical ANC duration, and ANC recovery through pairwise spearman correlation analysis.

RESULTS

This study included a population of 42 patients with breast cancer. The age of the patients varies between 31 and 70 years, with a mean age of 50.8 ± 9.8 years. The number of patients with stage II, III, and IV breast cancer included in this study were 15 (35.7%), 24 (57.1%), and 3 (7.1%), respectively. Four (9.5%) geriatric patients were included in this study (**Table 1**). No bone pain complaint was observed during filgrastim administration.

Table 1. Patient baseline characteristic.

	n	%
Age (years)	52 (41.2 – 57.5)	
Geriatric status		
Non-geriatric (<60 years old)	33	78.6
Geriatric (≥60 years old)	9	21.4
Breast cancer staging		
II	15	35.7
III	24	57.1
IV	3	7.1
Grade of Neutropenia		
Grade 0 (no neutropenia)	1	2.4
Grade 1	0	0
Grade 2	0	0
Grade 3	3	7.14
Grade 4 (critical ANC, <500/mm^3)	38	90.5
Incidence of Febrile Neutropenia		
Non febrile neutropenia	40	95.2
Febrile Neutropenia	2	4.8
Duration of ANC reaching >10000/mm^3 from the start of filgrastim administration (days)		
Mean	9.57±0.70	
Median (min-max)	10 (8-11)	
Days		
8	2	4.8
9	17	40.5
10	20	47.6
11	3	7.14%

Slope Duration from Peak (Day 2) Until Nadir		
Mean	4.3±0.5	
Median (min-max)	4 (3-5)	
Days		
3	1	2.4
4	27	64.3
5	14	33.3
Mean	6.3±0.5	
Median (min-max)	6 (5-7)	
Days		
5	1	2.4
6	27	64.3
7	14	33.3
Critical ANC (<500/mm^3) duration (days) (n = 38)		
Mean	1.9±0.6	
Median (min-max)	2 (1-3)	
Days		
1	9	23.7
2	25	65.8
3	4	10.5
Duration from Nadir Until ANC>10000/mm^3 (days) (n=42)		
Mean	3.3±0.8	
Median (min-max)	3 (1-5)	
Days		
1	1	2.4
2	5	11.9
3	19	45.2
4	16	38.1
5	1	2.4

All the participants were patients with stage II (15/42), III (24/42), and IV (3/42) breast cancer under the care of Hematology-Medical Oncology Department of Internal Medicine, Dr. Soetomo General Teaching Hospital, Surabaya, Indonesia who received TAC chemotherapy. The age of the patients varied between 31 and 70 years. The mean age was 50.8 ± 9.8 years, hence the results of this study are limited to middle-aged and geriatric patients without the representation of stage I breast cancer.

Neutropenia Grading and Febrile Neutropenia Incidence

Out of the 42 patients, 41 (97.6%) patients had neutropenia. Two incidences of FN occurred during filgrastim administration in patients with grade IV neutropenia. A difference in the duration of FN between the two patients was observed; the patient with a lower nadir (70/mm^3) experienced two days of FN, whereas the other patient with 150/mm^3 nadir recovered immediately. Both patients with FN eventually stabilized and their ANC recovered to more than 10000/mm^3.

ANC Evaluation

The evaluation of ANC in this study suggested a requirement for a similar duration of filgrastim administration to reach 10000/mm^3 of ANC with a similar response to filgrastim (p = 0.968). The duration of the critical ANC (<500/mm^3) or stage IV neutropenia detected in this study ranged between 1 and 3 days with an average of 1.9 ± 0.6 days and a median of two days. A patient with 2770/mm^3 ANC nadir point was the highest among the participants.

Based on this study, the evaluation of ANC slope and recovery duration did not show a significant difference. However, we discovered that the depth of nadir is inversely correlated with ANC recovery duration and ANC slope duration both with fair strength, r = −0.489 and r = −0.438 (p <0.05), respectively. Based on this result, it is suggested that nadir as the lowest point of ANC should be noted as a pivotal milestone for ANC slope and recovery evaluation as the correlation suggests in patient with lower ANC nadir could prolong both ANC slope and recovery which eventually resulting in longer duration of filgrastim administration.

Assessment of ANC Parameter Correlation to Age

The correlation analysis of highest grade of neutropenia - age (p = 0.274); critical ANC duration - age (p = 0.126), and ANC recovery duration – age (p = 0.608) did not show any significant result. These results suggest that age was not correlated with neutropenia severity and ANC recovery, which implicate that filgrastim administration in breast cancer patient receiving TAC chemotherapy still provide a comparable recovery regardless of age.

DISCUSSION

This study evaluated the implementation of extended filgrastim administration based on a higher target of ANC 10000/mm^3 as compared to recommendations of target ANC that vary between post nadir[13] and 2000–3000/mm^3.[15] The duration of treatment to reach >10000/mm^3 ANC in this study was 8–11 days, with an average of 9.6±0.7 days. The majority of the patients (41/42) in this study suffered from CIN; however,

FN only occurred in two (4.8%) patients with zero incidence of sepsis. A previous study also reported 9.8 ± 0.8 days of administration with a target ANC of 5000/mm^3, that showed a faster ANC recovery in this study population even with higher ANC target compared to previously reported study.[10] This difference might be caused by distinct responses of the population toward the myelosuppressive effect of filgrastim or chemotherapy, which is yet to be explained.[10] Further studies regarding the pharmacogenomics or epigenetics of the involved drugs should also be conducted. Nonetheless, it may be preferable to achieve a higher ANC target in a shorter duration to obtain better protection against infections.[16]

The critical ANC duration in this study lasted for an average of 1.9 ± 0.6 days, with a median of two days. A similar study in Korea within breast cancer patients receiving TAC chemotherapy showed an average critical ANC duration of 2.48 ± 1.03 days in patients receiving TAC and daily filgrastim administration.[10] During the duration of critical ANC, patients are vulnerable to FN and infections,[16] and thus, achieving a shorter duration of critical ANC is favored. A multi-center study in Canada showed that a 5-day filgrastim administration was not inferior to 7 and 10-days administration in terms of preventing FN.[17] Investigation of the correlation between filgrastim administration and critical ANC duration requires further study, especially in similar settings as the dynamics of ANC during chemotherapy and filgrastim administration was not evaluated in prior study and therefore this study could provide a better understanding of ANC slope and recovery to fill the gap of previous study limitation. However, limitation of this study lies in the absence of control group with ANC target of ≥ 5000/mm3 with comparison to previously reported study.

Beside the clinically overt adverse effects, the myelosuppressive effects of chemotherapy could lead to the occurrence of CIN.[18] CIN condition further prompts the occurrence of FN and sepsis. These unfavorable events worsen the overall prognosis of patients with breast cancer. The novel approach of filgrastim administration could potentially minimize the mortality and morbidity caused by the myelosuppressive effects of chemotherapy.[19] The TAC chemotherapy regimen has been classified as high-risk for inducing FN.[20] A study involving 61 patients receiving the TAC chemotherapy regimen along with pegfilgrastim prophylaxis also reported CIN incidence within the participants at least during one cycle.[9] An Indonesian study also reported neutropenia occurring in 98% of patients receiving the TAC chemotherapy along with filgrastim administration.[8] This result confirmed and emphasized that the TAC chemotherapy regimen has a high risk of inducing CIN, even when combined with filgrastim administration.

The nadir was observed 5–7 days post chemotherapy and commonly seen on the 6th day (**Figure 1**), demonstrating an earlier nadir than a previous study, which suggested the 7th day as the most common day for nadir.[9] The nadir ANC median was 155/mm^3 with a similarity across all the patients (p >0.05). On a closer look, the patient with a high outlier nadir ANC (2770/mm^3) presented with asthma as a co-morbidity. The lung tissues of patients with asthma are known to produce a higher level of G-CSF, and thus, they have a higher G-CSF level in their circulation.[21] This effect was shown to be able to ameliorate the myelosuppressive effect of chemotherapy and protect the patient from neutropenia. However, besides its benefits, this observation also suggests that filgrastim administration could trigger asthma exacerbation, which is an important point for clinical practice.

The result of this study revealed a similar change in ANC among patients, commencing with an increasing ANC, which consistently reached its peak after two days following chemotherapy. After reaching its peak on the 2nd day post chemotherapy, ANC then decreased until it reached the lowest point of ANC or the nadir point, which can be observed around 5–7 days post chemotherapy. The nadir point should be the primary focus of the clinician when giving care to patients receiving myelosuppressive chemotherapy, without overlooking the tendency of critical ANC alongside the nadir point as it could lead to FN or dire infection including sepsis. Moreover, this study revealed that the critical ANC duration lasted for 1 day in 9 patients (23.7%), 2 days in 25 patients (65.8%),

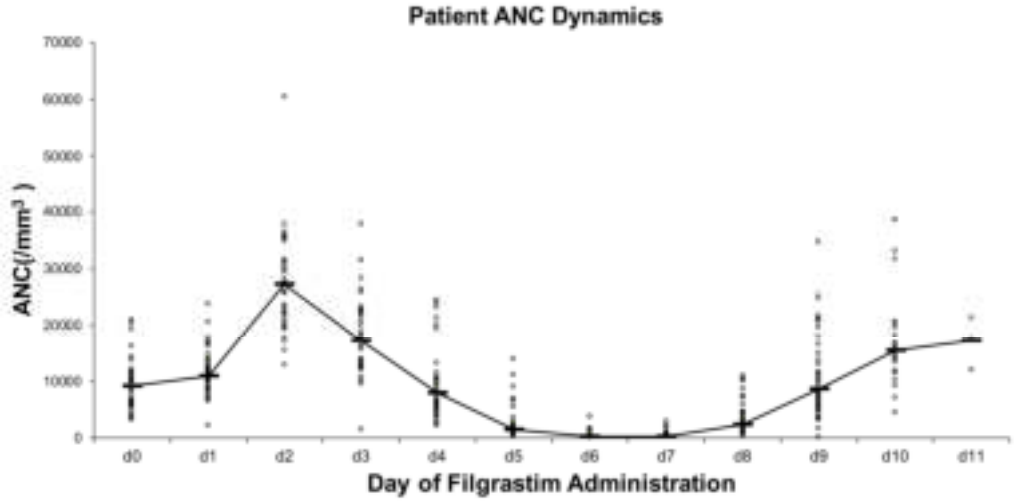

Figure 1. Curve of patients ANC during filgrastim administration. ANC: absolute neutrophil count; d0 = chemotherapy administration; d1: day 1 of filgrastim administration.

and 3 days in 4 patients (10.5%).

All the patients were treated in a non-sterile room and there were zero incidences of sepsis. The maintenance of the immune system, including ANC control, in patients undergoing chemotherapy is critical in preventing infection, especially in a tropical country like Indonesia. The target ANC recommended from various guidelines as an indication to stop filgrastim administration varies between post nadir and 2000–3000/mm^3.[13,15] However, to the best of our knowledge, the available guidelines were not generated based on studies conducted in Indonesia. This study used 10000/mm^3 as ANC for prevention of infections. Further study is required to compare target ANC values for prevention of FN and infections as well as for survival and therapeutic response in the same settings.

The nadir depth (ANC during nadir) was inversely correlated with the duration of ANC recovery to >10000/mm^3 with fair strength (r = −0.489, p <0.05). Also, the duration of ANC slope from the ANC peak in the 2nd day until reaching nadir is inversely correlated with ANC recovery duration with fair strength (r = −0.438, p <0.05). This finding suggested that the depth of nadir and the duration to reaching nadir from the 2nd day can be used to predict ANC recovery and help clinicians monitor patients with a tendency of longer ANC recovery.

Out of the 42 patients, there were two incidences of FN in patients with grade IV neutropenia. FN lasted for 1–2 days and immediately recovered, reaching >10000/mm^3 ANC. Patients with lower ANC exhibited a longer duration of FN (two days), which further emphasized the importance of monitoring patients with low ANC.

Clinical Applicability

Clinical applicability of this study suggests that the time-point of ANC nadir post-chemothrapy during filgrastim administration could be measured during 5-7 days post-chemothrapy that could predict ANC recovery duration. Furthermore, measurement of 2nd day and nadir duration could also predict ANC recovery duration. With a more caution focused on patient with a faster ANC slope and lower nadir.

Extrapolation of the Results to Target Population

This study was performed in Dr. Soetomo Teaching Hospital in Surabaya, Jawa Timur, Indonesia as representation of the ethnicity. Therefore, this study might provide a data from population that could be comparable to Indonesia national settings compared to prior study in different ethnicity background.

Suggestion for Further Research

Based on this study in a limited sampling-frame, it is suggested that multi-center study in Indonesia could be performed to further confirm these findings and additional control group could further explain benefit of proposed extended filgrastim administration together with modified ANC target.

CONCLUSION

Extended filgrastim administration after TAC chemotherapy could ameliorate FN incidence and minimize its duration. However, CIN still occurs in breast cancer patient receiving filgrastim primary prophylaxis regardless of age and neutropenia severity. Nadir as the lowest point of ANC should be noted as a pivotal milestone for ANC slope and recovery evaluation

CONFLICT OF INTEREST

This study was a part of the DAGCSF_NP_III Study (ClinicalTrials.gov: NCT03343145 funded by Dong-A ST Co., Ltd. through Prodia the CRO in Indonesia without any restriction in reporting the results.

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Predictors of In-Hospital Mortality in Patients with Acute Coronary Syndrome in Hasan Sadikin Hospital, Bandung, Indonesia: A Retrospective Cohort Study

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ABSTRACT

Background: *Acute coronary syndrome (ACS) is a world health problem with a high mortality rate and is expected to continue to rise in number. The high ACS mortality rate in the hospital is influenced by demographic characteristics, cardiovascular risk factors, clinical presentation, and management. This study aimed to determine the predictors of ACS death at Dr. Hasan Sadikin Hospital Bandung as the highest referral center in West Java.* ***Methods:*** *This study is a retrospective cohort study on all ACS patients undergoing treatment at Dr. Hasan Sadikin Hospital Bandung from January 2018 to December 2019. Multivariate analysis was performed using a logistic regression test with the backward method to assess predictors of patient outcomes.* ***Results:*** *This study involved 919 patients with the in-hospital mortality rate was 10.6%. Multivariate analysis showed that age >65 years was a demographic factor that play a role as a predictor of mortality mortality (AOR 2.143; 95% CI = 1.079-4.256; p = 0.030). Clinical presentation of cardiac arrest arrest (AOR 48.700; 95% CI =14.289-165.980; p<0.001), SBP <90 mmHg (AOR: 4.972; 95% CI =1.730-14.293; p=0.003, heart rate >100 beats per minute (AOR 4.285; 95% CI =2.209-8.310; p<0,001), cardiogenic shock (AOR: 5.433; 95% CI= 2.257-13.074; p<0.001). Cardiovascular management can reduce the risk of in-hospital mortality. Multivariate analysis showed statins (AOR 0.155; 95% CI=0.040-0.594; p=0.007), beta blockers (AOR 0.304; 95% CI=0.162-0.570; p<0,001) and Percutaneous Coronary Intervention (AOR 0.352; 95% CI=0.184-0.673; p=0.002) significantly reduce in-hospital mortality. Interestingly, smoking is associated with a lower mortality rate (OR 0.387; p <0.001).* ***Conclusion:*** *Clinical presentation of cardiac arrest has the highest risk of death, the sequence is cardiogenic shock, heart rate >100 beats per minute, and age >65 years. Administration of statins, beta-blockers, PCI, and smoking are factors that reduce the risk of death.*

Keywords**:** *Hospital death, predictor, acute coronary syndrome.*

INTRODUCTION

Acute coronary syndrome (ACS) is a worldwide health problem with a high mortality rate and its prevalence is expected to continue to increase. The World Health Organization (WHO) states that cardiovascular disease is a global cause of death worldwide.[1]

The high ACS mortality rate in the hospital is influenced by many factors, such as demographic factors, history of cardiovascular risk factors, clinical presentation, and the results of investigations and management in the hospital.[2-4]

Several studies have shown that the mortality rates in ACS patients vary among countries

around the world.[5,6] There was no national data on the incidence and mortality of ACS in Indonesia. Research on predictors of mortality in Dr. Hasan Sadikin Hospital Bandung, which is the highest referral center hospital in West Java, has never been done. This study aimed to analyze the data regarding the mortality predictor of hospital care in ACS patients at Dr. Hasan Sadikin Hospital Bandung. Hence, hopefully the results of our study can substantially fill the gap of data regarding predictor of mortality in ACS patients in Indonesia.

METHODS

This is a retrospective cohort study on ACS patients who underwent treatment at Dr. Hasan Sadikin Hospital Bandung from the period of January 2018 to December 2019. All ACS patients such as unstable angina pectoris (UAP), ST-elevation myocardial infarction (STEMI), and Non-ST Elevation Myocardial Infarction (NSTEMI) were included. The inclusion criteria of this study were medical records from male and female subjects aged ≥18 years and diagnosed with ACS. Incomplete medical records, ACS triggered or associated with comorbid accidents, trauma, surgery, or procedures were excluded from the study

Data such as identity, history, physical examination, ECG, laboratory, medical therapy during hospital care, revascularization measures, complications during treatment, final diagnosis, and discharge status were included. Hospital deaths are deaths due to all causes of death, both cardiovascular and non-cardiovascular deaths.

Ethics approval and consent to participate was assigned by Medical Research Ethics Committee Dr. Hasan Sadikin Hospital.

Statistical Analysis

The normality test was carried out on numerical data. Data with normal distribution are expressed as means. Data with an abnormal distribution are expressed in medians with minimum and maximum percentages. Bivariate analysis using unpaired T-test or Mann-Whitney analysis. Variables with a p-value less than 0.25 in the bivariate analysis were included in the logistic regression analysis. Multivariate logistic regression analysis was performed by using the backward method. The analysis was continued with the main interpretation of the predictive conceptual framework to determine which variables were related to the dependent variable. Significance was determined based on a p-value <0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows Operating System, version 24.0 software (IBM Corp., Armonk, N.Y., USA).

RESULTS

This study involved 919 patients, with 76% of the study subjects being male with a mean age of 59 ± 11 years. The ACS mortality rate in the hospital was 10.6%. The most common cardiovascular risk factors found were smoking (71.4%), followed by hypertension (64.6%), diabetes mellitus (22.4%), dyslipidemia (19.4%). The percentage of cardiac arrest upon arrival at the hospital was 3.5%. Management of revascularization was not entirely carried out on study subjects. A total of 469 study subjects received revascularization therapy (PCI), consisting of 319 patients with a diagnosis of STEMI (59.6%) and 150 patients with a diagnosis of NSTEMI/UAP (39.1%), while 412 patients (44.8%) %) did not receive revascularization therapy (**Table 1**).

Death in care occurred more frequently in female subjects as much as 16.3% (OR 1.996; p=0.002), old age >75 years (OR 7.069; p <0.001). Smoking is a cardiovascular risk factor associated with a lower mortality rate (OR 0.387; p <0.001). Other cardiovascular risk factors were not statistically significant for the risk of death during treatment (p>0.05) (**Table 1**).

Clinical presentation of cardiac arrest (OR 49.051; p <0.001), SBP <90 mmHg (OR 14.476; p <0.001), heart rate > 100 beats per minute (OR 7.717; p <0.001), clinical class of cardiogenic shock (OR 16.752; p <0.001) on arrival at the emergency room were associated with high mortality rates. ECG with ST segment elevation (OR 2.023; p = 0.003), abnormal renal function with a creatinine value >2.0 mg / dL (OR 5.507; p <0.001), troponin-I ≥9.0 ng / dL (OR 2.027; p <0.028) and a random blood glucose ≥200 mg / dL (OR 4.080; 95% CI =

2.175-7.656; p <0.001) were also associated with higher mortality during treatment. Management of revascularization and hospital-administered drugs, such as dual antiplatelets (OR 0.111; p <0.001), anticoagulants (OR 0.524; p = 0.022), ACE-inhibitors (OR 0.184; p <0.001), beta blockers (OR 0.170; p <0.001) and statins (OR 0.089; p <0.001) were associated with lower hospital mortality (**Table 1**).

Table 1. Baseline characteristic of study population.

Variables	Total n=919	Death n=98	Alive n=821	Crude OR (95% CI)	p-value
Demographic factors					
Sex. n (%)					
Female	221 (24.0)	36 (16.3)	185 (83.7)	1.996 (1.283 – 3.106)	0.002
Male	698 (76.0)	62 (8.9)	636 (91.1)	1	
Age (years)	59 ± 11	65 ± 11	58 ± 10		
<65	663 (72.1)	49 (7.4)	614 (92.6)	1	
65-75	195 (21.2)	27 (13.8)	168 (86.2)	2.014 (1.222 – 3.320)	0.006
>75	61 (6.7)	22 (36.1)	39 (63.9)	7.069 (3.887 – 12.856)	<0.001
BMI (kg/m^2)	23.4 (15.6 – 44.4)	23.4 (16.3 – 44.4)	23.4 (15.6 – 36.7)		
<18.5	22 (2.4)	2 (9.1)	20 (90.9)	0.758 (0.167 – 3.449)	0.720
18.5-22.9	206 (22.4)	24 (11.7)	182 (88.3)	1	
23.0-27.4	597 (65.0)	67 (11.2)	530 (88.8)	0.959 (0.584 – 1.574)	0.867
≥27.4	94 (10.2)	5 (5.3)	89 (94.7)	0.426 (0.157 – 1.154)	0.093
Cardiovascular History and Risk Factors, n (%)					
Smoking	656 (71.4)	51 (7.8)	605 (92.2)	0.387 (0.253 – 0.593)	<0.001
Diabetes Mellitus	206 (22.4)	27 (13.1)	179 (86.9)	1.364 (0.850 – 2.189)	0.197
Hypertension	594 (64.6)	63 (10.6)	531 (89.4)	0.983 (0.635 – 1.522)	0.939
Dyslipidemia	178 (19.4)	13 (7.3)	165 (92.7)	0.608 (0.331 – 1.117)	0.106
History of angina	329 (35.8)	37 (11.2)	292 (88.8)	1.099 (0.713 – 1.694)	0.669
History of premature CAD	73 (7.9)	4 (5.5)	69 (94.5)	0.464 (0.165 – 1.300)	0.135
History of PCI	110 (12.0)	6 (5.5)	104 (94.5)	0.450 (0.192 – 1.053)	0.059
History of CABG	6 (0.7)	0 (0.0)	6 (100.0)	0.637 (0.036 – 11.392)	0.759
Clinical Presentation					
First medical contact (hour)				1.006 (1.000 – 1.012)	0.054
Onset of hospital arrival (hour)	10 (0.3-288)	10 (0.33-228)	12 (20-240)	1.000 (1.000 – 1.000)	0.578
Cardiac arrest. n (%)	32 (3.5)	26 (81.3)	6 (18.8)	49.051 (19.551 – 123.060)	**<0.001**
SBP (n (%)					
<90 mmHg	45 (4.9)	26 (57.8)	19 (42.2)	14.476 (7.550 – 27.756)	**<0.001**
90-139 mmHg	660 (71.8)	57 (8.6)	603 (91.4)	1	
140-159 mmHg	140 (15.2)	10 (7.1)	130 (92.9)	0.814 (0.405 – 1.636)	0.563

160-179 mmHg	63 (6.9)	3 (4.8)	60 (95.2)	0.529 (0.161 – 1.740)	0.295
≥180 mmHg	11 (1.2)	2 (18.2)	9 (81.8)	2.351 (0.496 – 11.143)	0.282
Heart rate (n (%))					
<60 bpm	69 (7.5)	11 (15.9)	58 (84.1)	2.820 (1.386 – 5.738)	**0.004**
60-100 bpm	730 (79.4)	46 (6.3)	684 (93.7)	1	
>100 bpm	120 (13.1)	41 (34.2)	79 (65.8)	7.717 (4.770 – 12.485)	**<0.001**
Heart Failure. n(%)					
No heart failure	653 (71.1)	35 (5.4)	618 (94.6)	1	
Heart Failure	190 (20.7)	26 (13.7)	164 (86.3)	2.779 (1.638 – 4.784)	**0.016**
Cardiogenic shock	76 (8.2)	37 (48.7)	39 (51.3)	16.752 (9.529 – 29.449)	**<0.001**
ECG presentation, n (%)					
Persistent ST segment elevation	535 (58.2)	71 (13.3)	464 (86.7)	2.023 (1.272 – 3.218)	**0.003**
ST segment depression, non-persistent ST elevation, abnormality of T wave	384 (41.8)	27 (7.0)	357 (93.0)	1	
Laboratorium Values					
Troponin (n, %)					
<0.4 (ng/dL)	185 (20.1)	13 (7.0)	172 (93.0)	1	
0.4 - <1.0 (ng/dL)	84 (9.1)	9 (10.7)	75 (89.3)	1.588 (0.651 – 3.874)	0.310
1.0 - <2.0 (ng/dL)	65 (7.1)	6 (9.2)	59 (90.8)	1.346 (0.489 – 3.700)	0.565
2.0 - <5.0 (ng/dL)	90 (9.8)	9 (10.0)	81 (90.0)	1.470 (0.604 – 3.580)	0.396
5.0 - <9.0 (ng/dL)	66 (7.2)	4 (6.1)	62 (93.9)	0.854 (0.268 – 2.717)	0.789
≥ 9.0 (ng/dL)	429 (46.7)	57 (13.3)	372 (86.7)	2.027 (1.081 – 3.802)	**0.028**
Creatinine (n, %)					
≤1.2 mg/dL	535 (58.2)	31 (5.8)	504 (94.2)	1	
>1.2 – 2.0 mg/dL	218 (23.7)	25 (11.5)	193 (88.5)	2.106 (1.212 – 3.659)	**0.008**
>2.0 mg/dL	166 (18.1)	42 (25.3)	124 (74.7)	5.507 (3.327 – 9.115)	**<0.001**
Random blood glucose (n, %)					
<110 mg/dL	289 (31.4)	18 (6.2)	271 (93.8)	1	
110-199 mg/dL	494 (53.8)	51 (10.3)	443 (89.7)	1.733 (0.992 – 3.029)	0.053
≥200 mg/dL	136 (14.8)	29 (21.3)	107 (78.7)	4.080 (2.175 – 7.656)	**<0.001**
In-Hospital Utilization of Medications and Interventions					
Pharmacological Therapy in the First 24 hours					
DAPT, n (%)	902 (98.2)	89 (9.9)	813 (90.1)	0.111 (0.042-0.297)	**<0.001**
Anticoagulant, n(%)	786 (85.5)	75 (9.5)	711 (90.5)	0.524 (0.302-0.910)	**0.022**
ACE-inihibitor, n(%)	498 (54.2)	20 (4.0)	478 (96.0)	0.184 (0.110 – 0.307)	**<0.001**
Beta blocker, n(%)	574 (62.5)	25 (4.4)	549 (95.6)	0.170 (0.105 – 0.273)	<0.001
Statin, n(%)	895 (97.4)	85 (9.5)	810 (90.5)	0.089 (0.039 – 0.204)	**<0.001**

Revasculatization Therapy					
STEMI, n (%)					
PCI	319 (59.6)	27 (8.5)	292 (91.5)	0.361 (0.216 – 0.605)	**<0.001**
Fibrinolytic	117 (21.9)	7 (6.0)	110 (94.0)	0.352 (0.157 – 0.790)	**0.009**
Drugs	178 (33.3)	37 (20.8)	141 (79.2)	2.493 (1.503 – 4.134)	**<0.001**
NSTEMI/UAP, n (%)					
PCI	150 (39.1)	3 (2.0)	147 (98.0)	0.179 (0.053 – 0.604)	**0.002**
Drugs	234 (60.9)	24 (10.3)	210 (89.7)	5.600 (1.656 – 18.942)	0.006

OR: odds ratio; BMI: body mass index; STEMI: ST elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; ACE: angiotensin converting enzyme; DAPT: dual antiplatelet therapy; mg: milligrams; ng: nanograms; SBP: systolic blood pressure; CABG: coronary artery bypass surgery; CAD: coronary artery disease.

Multivariate analysis in this study showed that the factor associated with highest risk of death was cardiac arrest (AOR 48.700; 95% CI =14.289-165.980; p<0.001), then followed by clinical signs of cardiogenic shock (AOR: 5.433; 95% CI= 2.257-13.074; p<0.001), SBP <90mmHg (AOR: 4.972; 95% CI =1.730-14.293; p=0.003), heart rate >100 beats per minute (AOR 4.285; 95% CI =2.209-8.310; p<0,001) and age >65 years (mortality (AOR 2.143; 95% CI = 1.079-4.256; p = 0.030). Factors that reduced the risk of death were statins as statins (AOR 0.155; 95% CI=0.040-0.594; p=0.007), beta blockers (AOR 0.304; 95% CI=0.162-0.570; p<0,001) and PCI (AOR 0.352; 95% CI=0.184-0.673; p=0.002) were associated with a reduced risk of death. (**Table 2**)

Table 2. Multivariate analysis of mortality predictor in hospital care.

Variables	Coefficient B	S.E.	P Value	AOR	95% C.I. AOR	
					Min	Max
Age (years)						
<65 tahun				1		
65-75	0.762	0.350	**0.030***	**2.143**	**1.079**	**4.256**
> 75	1.596	0.426	**<0.001***	**4.931**	**2.139**	**11.365**
Smoking	-0.901	0.312	**0.004***	**0.406**	**0.220**	0.749
Cardiac arrest	3.886	0.626	**<0.001***	**48.700**	**14.289**	**165.980**
SBP (mmHg)						
<90	1.604	0.539	**0.003***	**4.972**	**1.730**	**14.293**
90-139				1		
140 – 159	-0.374	0.462	0.418	0.688	0.278	1.701
160 – 179	-1.004	0.715	0.161	0.366	0.090	1.489
≥180	-0.463	1.172	0.692	0.629	0.063	6.255
Heart rate (beats per minute)						
<60	-0.012	0.574	0.984	0.988	0.321	3.044
60 – 100				1		
>100	1.455	0.338	**<0.001***	**4.285**	**2.209**	**8.310**
Heart Failure						
No heart failure				1		
Heart Failure	0.546	0.353	0.122	1.727	0.864	3.450
Cardiogenic shock	1.692	0.448	**<0.001***	**5.433**	**2.257**	**13.074**
PCI	-1.044	0.330	**0.002***	**0.352**	**0.184**	**0.673**
Beta blockers	-1.192	0.322	**<0.001***	**0.304**	**0.162**	**0.570**
Statins	-1.867	0.687	**0.007***	**0.155**	**0.040**	0.594

S.E.: standard error; AOR: adjusted odds ratio; CI: confidence interval; SBP: systolic blood pressure; PCI: percutaneous coronary intervention.

DISCUSSION

The mortality rate of ACS in-hospital care in this study was 10.6% for all patients diagnosed with ACS. Indonesia does not have a national ACS mortality rate. Still, this number is higher when compared to the mortality rate in other Asian countries (5%)[7,8] and developed countries such as America and Europe, which is 4-8%.[9–12]

Regarding demographic data, most of the participants were male (76%) with age below 65 years (72.1%). Consistently, ACS registry data from Brazil conducted by Santos et al. also showed similar results.[13] ACS patients in our registry were more likely overweight (65%) and smokers (71.4%). Similarly, Mohanan et al. study stated that ACS patients were more likely overweight but Santos et al. study found that ACS patients were less likely smokers.[13,14] Moreover, in concern to comorbidities, history of diabetes mellitus, hypertension, dyslipidemia, and angina in our participants were 22.4%, 64.6%, 19.4%, and 35.8%, respectively. Nonetheless, Santos et al. study found that although the prevalence of prior diabetes mellitus, hypertension and angina in ACS patients were comparable to our results, the dyslipidemia occurs in half of ACS patients (53.1%).[13]

Prior revascularization procedure including PCI and CABG were performed in 12% and 0.7%, respectively of our participants. In contrast, Santos et al.[13] study revealed the prevalence of history of PCI was two times higher as opposed to our results and history of CABG was 23.6%. The explanation behind this various data is because our hospital still has limited resources and facilities.

In regard to clinical presentation, mean onset of chest pain duration at admission was 10 (0.3-288) hours. Furthermore, cardiac arrest, heart failure, clinical signs of cardiogenic shock were present in 3.5%, 20.7%, and 8,2%, respectively in our participants. Moreover, ACS data from Nigeria also revealed the similar results to ours.[15] Our participants more apparently had normal SBP with range of 90 to 139 mmHg (71.8%), normal HR with range of 60 to 100 bpm (79.4%) and ST-segment elevation on ECG (58.2%). Similar to our results, ACS registry from India and Nigeria revealed that ACS patients prone to had normal SBP and HR, and presented with STEMI.14,15 However, in Brazil, unstable angina was the most common presentation of ACS.[13] Concerning laboratory values at admission, our participants had troponin I levels equal or higher than 9 ng/dL (46.7%), creatinine equal or lower than 1.2 mg/dL (58.2%), and normal random blood glucose (53.8%). Consistently, Mohanan et al. study demonstrated similar results to ours.[14]

Furthermore, the majority of our participants received DAPT (98.2%), anticoagulant (85.5%), ACE inhibitor (54.2%), beta-blocker (62.5%), and statin (97.4%). Expectedly, ACS patients in Nigeria also demonstrated similar findings to ours.[15] In revascularization therapies, 59.6% and 21.9% of STEMI patients underwent PCI and fibrinolytic procedures, respectively. Whereas 39.1% of NSTEMI/UAP patients underwent PCI. Interestingly, in India, fibrinolytic were more often performed compared to PCI.[14] Whereas ACS registry in Brazil showed the opposite results.

This study showed that old age (>65 years old) was a consistent predictor of mortality, similar to the results from various examining predictors of mortality and other cardiovascular outcomes.[2] Patients with old age were associated with atypical symptoms, metabolic disturbances, more cardiovascular risk factors or comorbidities, complex coronary lesions, possible decreased ventricular function, decreased and impaired renal function, a high risk of bleeding, which increased the risk of complications after revascularization (PCI or CABG).[16–18]

Several studies have linked female sex to cardiovascular outcomes in ACS patients, but it turns out that the mortality rate in women occurs at non-unadjusted assessments. The female mortality rate decreased after multivariable adjustment. This multivariate adjustment had been made to age, comorbidities, and management.[19,20] Excess body mass index (BMI) was not associated with increased mortality in ACS patients. Following previous studies, Steinberg et al., Niedziela et al., and Kosuge et al. state that the excess body weight is not associated with death, known as the obesity paradox".[21–23]

Smoking in this study was independently and significantly associated with a reduction

in mortality rate in ACS patients. These results support the smoker's paradox theory.[24] A randomized controlled trial conducted by Zahger et al study found that current smokers were presented with a higher incidence of thrombolysis in myocardial infarction (TIMI) flow grade III in 90 minutes post PCI compared to non-smokers.[25] The underlying pathogenesis of ACS in smokers was different compared to non-smokers. Haematocrit and fibrinogen levels were significantly higher in the smokers' population which eventually predisposes thrombogenic obstruction with minimal underlying atherosclerotic narrowing. On the contrary, the non-smokers' population were predominated with atherosclerotic narrowing condition.[26,27] Therefore, administration of thrombolysis and/or anti-coagulant in smokers' population with ACS resulted in greater favorable outcomes and eventually reduced mortality risk compared to non-smokers.[24] Nevertheless, larger observational studies are still needed to confirm this smoker's paradox theory.

The risk factors of hypertension in this study were not related to the risk of death. Another study states that blood pressure at the time of hospital admission influences the increased risk of death in hospitals. This low mortality rate in patients with hypertension is also associated with the administration of therapies such as ACE inhibitors or angiotensin receptor blockers (ARBs) and post-ACS statins.[28–31]

Presentation of cardiac arrest on hospital admission was one of the predictors of death in the hospital. Patients with cardiac arrest were less likely to receive inadequate management, including aspirin, beta-blockers, statins, and ACE inhibitors, than patients without these complications. Patients were also more likely to experience other complications such as recurrent ischemia, cardiogenic shock, heart failure, kidney failure, stroke, and major bleeding.[32]

Increased heart rate (>100 beats per minute) was a predictor of hospital death. Increased heart rate is associated with decreased diastolic filling time, increased myocardial oxygen consumption, which can worsen ischemia and increase the risk of developing malignant arrhythmias. These results were consistent with previous studies.[33–37] Blood pressure <90 mmHg on hospital admission was a predictor of death in ACS patients. Blood pressure on admission was inversely associated with hospital death and was related to the extent of myocardial damage.[38,39]

Myocardial infarction complicated by cardiogenic shock is still a major problem in ACS management with high morbidity and mortality. The poor prognosis was thought due to complex coronary lesions, ventricular dysfunction, and a large infarct area. Patients with acute heart failure were less likely to receive optimal treatment compared with patients without heart failure.[40,41] In line with this study, multivariate analysis showed that cardiogenic shock was a predictor of death in ACS during treatment.

Meanwhile, ECG and increased troponin and creatinine values were not predictors of death in ACS patients. This result was slightly different from the GRACE registry, which stated that ST-segment deviation, increased troponin value, and creatinine value at presentation are predictors of mortality in ACS.

Pharmacological treatment, such as beta-blocker administration, had been shown to reduce the mortality rate in the literature.[42] Statin effects stabilizing unstable plaque and increasing collateralization in severe CAD.[43,44] Administration of statin in hospitals is associated with a reduced short-term mortality rate among patients after ACS.[45] Revascularization aims at restoring blood flow to ischemic myocardium. Percutaneous coronary intervention (PCI) is proven to reduce mortality rate, recurrent infarction, and stroke in ACS patients.[46] Consistently, our analysis showed that PCI and administration of beta-blocker and statin significantly and independently reduced the risk of in-hospital mortality in ACS patients. Additionally, mechanical support device such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was recommended by the European Society of Cardiology (ESC) as a final resort of therapy in ACS patients with cardiogenic shock who did not respond to vasopressor and inotropic administration.[47] Hence, despite of all aforementioned factors that associated with increased risk of mortality, unavailability of V-A ECMO in our center may

also be responsible for increased risk of mortality especially in ACS patients who presented with cardiogenic shock.

This study had several limitations. First, this study was a single-center, retrospective study with a relatively small sample size. Thus, the results of this study could not be extrapolated from findings in other research centers, hospitals, or even communities. Second, there was no further sub-analysis of the other variables for hospital death.

CONCLUSION

Clinical presentation of cardiac arrest has the highest risk of death, then sequentially followed by cardiogenic shock, SBP <90 mmHg, heart rate >100 beats per minute, and age >65 years. Administration of statin, beta-blocker, PCI, and smoking are factors that reduce the risk of death.

CONFLICT OF INTERESTS

Authors declare have no conflict of interests.

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Bedaquiline Effect on QT Interval of Drugs-Resistant Tuberculosis Patients: Real World Data

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ABSTRACT

***Background**: Bedaquiline (BDQ) is effective as part of treatment regimen for drug-resistant tuberculosis (DR-TB), but the cardiac safety profile of BDQ is not fully elucidated. This study aimed to analyse the cardiac safety of BDQ by examining its effect on the QT interval of DR-TB patients. **Methods**: This is a retrospective study cohort conducted in two DR-TB referral hospitals in Indonesia. The QT interval before and after therapy using BDQ was measured manually and corrected using the Fridericia formula (QTcF). The QT interval profile was analysed over time during BDQ treatment. **Results**: A total of 105 subjects participated in the study. The maximum mean difference (standard deviation) of QTcF after treatment with the baseline (ΔQTcF) is 34,06 (52,92) ms after three months of therapy. During BDQ treatment, clinically significant QTcF prolongations was observed in 37.1% subjects with neither arrhythmia nor any other adverse cardiac event occurred. The interval QT prolongation led to BDQ discontinuation in 15.2% subjects temporarily and in 6.7% subjects permanently. There were seven deaths (6.7%) during the treatment. **Conclusion**: During BDQ treatment, maximum QT prolongation was observed after three months of BDQ therapy. Therefore, more intensive cardiac monitoring is recommended during this period and afterwards.*

***Keyword**: bedaquiline, drug-resistant tuberculosis, QT interval prolongation.*

INTRODUCTION

Indonesia ranks among the 30 highest-ranking countries in the world when it comes to the burden associated with DR-TB, with the number of new cases increasing every year. In 2020, there were 8,200 new laboratory-confirmed DR-TB cases.[1] However, DR-TB treatment is still a challenge for clinicians due to the low effectiveness and the severe and life-threatening side effects.[2] These side effects may lead to additional morbidity, treatment withdrawal and even death of the patient.[3] In the last 50 years, a new TB drug has been developed from a new class of antibiotic, bedaquiline (BDQ). Clinical trials have shown that BDQ is effective in accelerating sputum conversion and improving success rate; however, BDQ may cause QT interval prolongation.[4] This poses a safety concern while using BDQ, as it may cause polymorphic ventricular tachycardia, also known as *Torsades de Pointes* (TdP), which may lead to sudden death.[5]

Another major concern is the long terminal half-life of BDQ (up to 5.5 months) due to tissue redistribution.[6]

This may lead to the generation of adverse effects of BDQ, including QT interval prolongation, which can last for a longer period or may even occur after the discontinuation of the drug.[4] Moreover, the cardiac safety profile of BDQ has not been fully elucidated by existing studies due to various limitations. Reports of drug-induced TdP were relatively rare, even though the drug is widely used.[5] Therefore, adequate data of cardiac safety of BDQ must be collected from all over the world, including Indonesia. The aim of this study was to analyse the effect of BDQ on the QT interval of DR-TB patients in pragmatic use from two DR-TB referral hospitals in Indonesia.

METHODS

This was a retrospective cohort study using real world data from patients' medical records. It was carried out at Dr. Saiful Anwar Malang Hospital (RSSA) and Dr. M. Goenawan Partowidigdo Cisarua Hospital (RSPG) between August 2020 and October 2020. Prior to its commencement, the study received ethical approval from the institutional review board in RSSA (No. 400/112/K.3/302/2020; April 6th 2020). All DR-TB patients who received BDQ as part of the treatment regimen were selected. The inclusion criteria were adult, aged >18 years, who were administered ECG before BDQ treatment and at least one ECG afterwards. Patients with unreadable ECG reports or incomplete medical records were excluded from the study. The QT intervals before and after the treatment were measured manually then were corrected to the heart rate using the Fridericia formula. According to the Indonesian technical guideline,[7] for cardiac safety monitoring during BDQ treatment, ECG should be performed on Day 2 (D2), in the first week (W1) and every month until the end of BDQ treatment (M1–M6).

The primary outcome was the QT interval profile consisted of QTcF, the difference of QTcF after treatment with the baseline (ΔQTcF) and the proportion of clinically significant QT prolongation over time during the BDQ treatment. The proportion of BDQ discontinuation related to adverse cardiac events was also considered as the primary outcome. According to the international harmonisation standard (ICH) clinical evaluation of QT/QTc interval prolongation and proarrhytmic potential for non-antiarrhytmic drugs (E14), clinically significant QT prolongation is defined as QTcF >500 ms, ΔQTcF >60 ms, or both.[8,9] However, as per WHO and the Indonesian guideline on DR-TB management, the criteria for the discontinuation of QT-prolonging drugs, including BDQ, are based on the absolute value of QTcF. The suspected drug should be interrupted for 7 to 14 days until the normal state is restored, if QTcF >500 ms in two measurements within 30-minute intervals and without cardiac symtoms.[10,11] This data of discontinuation was obtained from the clinician documentation on medical records.

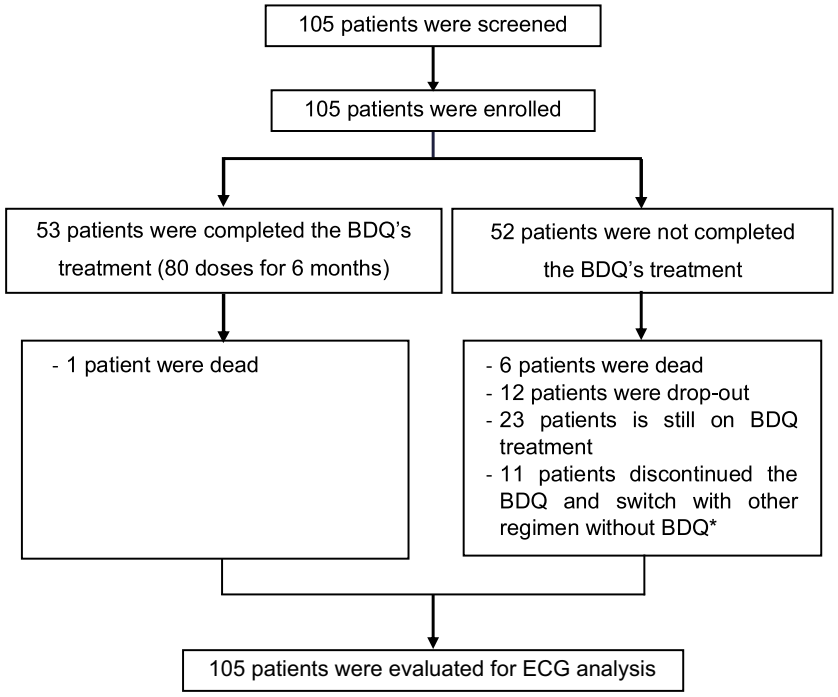
Based on formula of the mean difference between two paired groups (before and after), a minimum sample size of 66 subjects is necessary. The analysis of data was performed using SPSS software version 22. A t-test or Wilcoxon test was used to assess the difference in continuous variables, depending on the distribution of data.

RESULTS

Due to the ongoing COVID-19 pandemic in August to October 2020, there was limited mobility between regions in addition to limited data access to the study site. Therefore, it was not possible to carry out data selection as planned. Data were collected in a *convenient* manner, with support from data enumerators at RSSA. Due to the limited number of DR-TB patients treated with BDQ at each site, a small sample population of patients who received BDQ during the study period were finally selected. A total of 105 patients met the selection criteria (**Figure 1**). The baseline characteristics of the study subjects are presented in **Table 1**.

A total of 405 ECG reports from 105 subjects were analysed. During the six months of BDQ treatment, neither arrhythmia nor any other cardiac event occurred. The values of ΔQTcF tend to increase (Table 2), and its maximum values were observed after three months of the treatment (M3). The QT interval prolongation >500 ms during the treatment led to the interruption of BDQ treatment in 16 of the 105 subjects.

In this study, the prolongation of the QT interval was the common cause of the temporary



*The reason for switching the regiment in 11 patients:

- Failure of treatment (positive culture after BDQ treatment): 1 patient
- Adverse drug reaction:
  a. Persistence QT prolongation: 7 patients
  b. Inverted T wave with normal QT interval: 1 patient
  c. Renal impairment: 1 patient
  d. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome): 1 patient

Figure 1. Enrollment flowchart.

Table 1. Baseline characteristics of the subjects.

Variables	n (%)
Gender	
- Male	61 (58.1)
- Female	44 (41.9)
Age in years, median (minimum – maximum)	41 (18 – 68)
Comorbidity, n (%)	38 (36.2)
- Heart disease	1
- Kidney disease	3
- Subclinical hyperthyroidism	1
- Subclinical hypothyroidism	2
- DM	31
- Hypertension	2
- Asthma	1
Category of DR-TB, n (%)	
- MDR	79 (75.2)
- Pre-XDR	18 (17.1)
- XDR	8 (7.6)
Number of QT prolonging drugs, n (%)	
- One drug (BDQ)	2 (1.9)
- Two drugs	37 (35.2)
Lfx/BDQ	20
Mfx/BDQ	3
BDQ/Cfz	14

- Three drugs	65 (61.9)
Lfx/BDQ/Cfz	51
Mfx/BDQ/Cfz	14
- Four drugs	1 (1,0)
Lfx/BDQ/Cfz/Dlm	
Completing BDQ treatment (80 doses)	
- Yes	53 (50.5)
- No	52 (49.5)
QTcF baseline in ms, mean (sd)	414.52 (33.74)
Serum kalium baseline in mEq/L*, mean (sd)	4.02 (0.64)

DM: Diabetes mellitus; DR-TB: Drug Resistant Tuberculosis; MDR: Multi-Drug resistant, XDR: Extensively Drug Resistant; BDQ: bedaquiline; Lfx: levofloxacin; Mfx: moxifloxacin; Cfz: clofazimine; Dlm: delamanid; QTcF: QT corrected using Fridericia formula; sd: standard deviation. *was obtained from 96 subjects.

Table 2. QTcF interval profile during BDQ treatment.

Time of monitoring	ΔQTcF* ms Mean (sd)	p value (95%CI)	Temporary discontinuation of BDQ treatment** n/N (%)	Clinically significant QTcF prolongation n (%)
D2	3.55 (37.60)	0.671[W]	**1**/36 (2.8)	4/36 (11.1)
W1	19.76 (39.69)	0.002 (7.83 – 31.68)	**1**/45 (2.2)	6/45 (13.3)
W2	11.70 (41.67)	0.073 (-1.13 – 24.53)	**2**/43 (4.6)	5/43 (11.6)
M1	27.19 (45.65)	<0.001 (15.50 – 38.88)	**3**/61 (4.9)	10/61 (16.4)
M2	23.71 (37.51)	<0.001 (13.94 – 33.49)	**2**/59 (3.4)	10/59 (16.9)
M3	34.06 (52.92)	<0.001 (19.33 – 48.79)	**7**/52 (13.5)	13 /52 (25.0)
M4	22.52 (47.34)	0.003 (8.29 – 36.74)	-	8/45 (17.8)
M5	21.23 (33.26)	0.002 (8.58 – 33.8)	-	5/29 (17.2)
M6	23.97 (52.82)	0.011 (5.83 – 42.11)	-	8/35 (22.9)
Total			16/105 (15.2)	39/105 (37.1)

D: day 2; W: week; M: month; ΔQTcF: the difference of QTcF after treatment compared with baseline; sd: standard deviation; CI: confidence interval.
* the difference of QTcF after treatment with the baseline
**Discontinuation related to interval QT prolongation, if QTcF >500 ms[9,10]

discontinuation of BDQ treatment (95.8%). The prolongation of QT the interval was persistent and led to the permanent discontinuation of treatment in seven subjects (6.7%). However, most subjects with a regimen containing BDQ are still on treatment (70.4%). In total, there were seven deaths during the study period.

DISCUSSION

In this study, 53 of the 105 subjects had completed BDQ treatment for six months (80 doses). However, only three subjects (2.9%) had complete ECG data for each monitoring time. Even in developed countries such as the United States, monitoring during BDQ treatment is a challenge. In California, only three of 37 patients (8%) had complete ECG data at each point of monitoring.[12]

Recently, some studies have reported on the safety aspects of BDQ under programmatic conditions. These studies are from various countries, including Salhotra et al.[13] in India (2020), Gao et al.[14] in China (2021), Katrak et al.[12] (2021) in the United States, and Brust et al.[15] and Isralls et al.[16] (2021) in South Africa. The baseline characteristics of the subjects of this

study are similar to that of the participants of the aforementioned studies where BDQ was also used together with other QT-prolonging drugs in the DR-TB treatment regimen and the lengths of the BDQ treatment varied between subjects.

During the treatment with BDQ, clinically significant QTcF prolongation was observed in 37.1% of the subjects. Prolongation of QT and subsequent discontinuation of treatment temporarily and permanently by the clinician is in 15.2% and 6.7% subjects, respectively. Salhotra et al. reported a lower proportion of clinically significant QTcF prolongation (16.3%) compared to this study. Temporary discontinuation of BDQ treatment due to QT prolongation in the studies of Salhotra et al.[13], Gao et al.[14], Guglielmetti et al.[17] and Katrak et al.[12] amounted to 2.9%, 4.2%, 0.77% and 11%, respectively. Here, the variability effect of BDQ on subjects' QT interval from study to study is influenced by the subjects' baseline characteristics, with various risk factors. In this study, 61.9% of the subjects were on three QT-prolonging drugs (including BDQ), and 35.2% of the subjects had comorbidities related to QT interval prolongation, such as diabetes, hypertension, heart disease, kidney disease and hypothyroidism. These factors could have contributed to more cases of clinical significance in terms of QTcF prolongation as well as discontinuation of treatment.

According to ICH E14, the risk of TdP is associated not only with the absolute value of the QTc interval (QTcF > 500 ms) but also with ΔQTcF > 60 ms.[8,9] The incidence of ventricular arrhythmia increases by 5 to 7% for every 10 ms increase in QTc value.[18] The criteria for the discontinuation of treatment due to the prolongation of the QT interval may vary, depending on the level of risk and tolerance of the patient population, which is specific to the indication of the treatment.[8] According to WHO and the Indonesian technical guidelines,[10,19] ΔQTcF > 60 ms is an indicator of the need to perform ECG more often and manage other risk factors.[11,20] In this study, 38 subjects (36.2%) were detected with QTc > 60 ms. There were no reports of arrhythmia or other cardiovascular events in this group. A total of 24 of the 38 subjects (63.2%) continued the treatment; 17 of them completed the BDQ treatment. Additionally, 11 of them were also detected to have a QTc value > 500 ms; therefore, BDQ treatment in these subjects was temporarily discontinued. Finally, two subjects dropped out, and treatment in one subject was changed, as they experienced a failure of the BDQ treatment.

During BDQ treatment, seven subjects (6.7%) died (**appendix 1)**. The cause of death in one subject was not related to BDQ (sepsis and respiration failure). For the remaining (6/7; 85.7%), the cause of death could not be assessed, as they died at home, as reported by their families. It is difficult to establish the causal relationship of death with the prolongation of the QTc interval without recording the ECG at the time of the incident and evaluating complete the data before death. However, death in MDR-TB patients may occur due to various causes, including the progression of the TB itself, severity of comorbidities, and disease complications.[21] The use of cardiac holter monitoring could be an option for recording ECG in real time, although it will be limited by the cost.[22]

This study contributes to the literature by reporting the cardiac safety of BDQ in a systematic and complete manner. The QT interval profile was analysed over time during treatment in order to obtain a complete picture of the cardiac safety of BDQ. Most ECG machines can automatically calculate QTc intervals. Although it may seem practical, this automatic calculation can be inadequate due to inconsistencies in terms of the correction formula and algorithm used between ECG machine manufacturers. In addition, the ECG machine is not able to identify T and U waves when the two waves overlap. The U wave appears in hypokalemic conditions, which often occurs in DR-TB patients. Therefore, it is very important to identify these waves manually in order to calculate the QT interval correctly.[23]

This study has a few limitations. There were no assessments of the effect of genetic factors associated with QT prolongation, QT interval diurnal variation and the effect of the number of risk factors in each subject on QT-interval prolongation. In addition, the power of the study is diminished by the fact

that the number of subjects in each group at each monitoring was less than the targeted minimum sample size. Further cohort studies are required to evaluate the cumulative effect of QT prolongation due to the long elimination half-life of BDQ. Patients should be followed up with after the end of their treatment. This study could not assess this, as there was no ECG record after BDQ use (after six months). Furthermore, BDQ concentration was not measured.

CONCLUSION

Maximum QT prolongations were observed mostly after three months of BDQ therapy. Therefore, more intensive cardiac monitoring is recommended during this period and afterwards.

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Appendix 1. Clinical Data of Subjects Who Died during DR-TB Treatment with Regiment Containing Bedaquiline

Subject code	Sex/age (in year)	Weight (kg)	Comor-bidity	DR-TB cate-gory	DR-TB regiment	Clinical information	Period of death	Cause of death	QT interval during therapy	Supporting data
05	Male/59	59	DM on insulin	Pre-XDR	Lfx/Bdq/ Cfz/H/Z/E/ B6	Discontinued of BDQ in M4 due to decreasing liver function (SGOT/SGPT 775/337)	M5	Unknown	QTcF (ms): M2: 454,57 M3: 446,29 M4: 470,91 ΔQTcF (ms): M2: -29,98 M3: -38,56 M4: -13,94	Serum kalium (mEq/L): M2: 3,2 M3: 3,6 eGFR: M3: 83 ml/min
09	Female/36	56	DM on insulin	XDR	Lfx/Bdq/ Lnz/Cs/ Eto/H/Z/E/ B6	Had received full dose (80 doses)	M7	Respira-tory failure and sepsis	QTcF (ms): W1: 431,27 W2: 422,81 M1: 464,16 M3: 447,68 M5: 466,64 M6: 421,47 ΔQTcF (ms): W1: -39,64 W2: -48,10 M1: -6,75 M3: -23,23 M5: -4,27 M6: - 49,44	Serum kalium (mEq/L): - M1: 4,0 - M3: 4,0 - M5: 3,9 - M6: 3,5 eGFR: 119 ml/ min
23	Female/25	42	-	MDR	Lfx/Bdq/ Lnz/Cfz/ Cs/B6	On day 5, Lnz was switch to E due to anemia. However, BDQ was continued. Treatment duration: 25 days	D25	Unknown	On D2: QTcF:434,24 ms ΔQTcF: 50,2 ms No subsequent ECG data.	On day 5, the Hb subject was 6,6 mg/dl
25	Male/28	48	-	Pre-XDR	Bdq/Lnz/ Cfz/Eto/E/ B6	Total treatment duration: 15 weeks	M4	Unknown	QTcF (ms): - M1: 403,11 - M2: 428,34 ΔQTcF (ms): - M1: 0,00 - M2: 25,23 No subsequent ECG data.	Serum kalium: - M1: 3,5 - M2: 3,4 eGFR: M2: 81,8 ml/ min

Appendix 1. Clinical Data of Subjects Who Died during DR-TB Treatment with Regiment Containing Bedaquiline

Subject code	Sex/age (in year)	Weight (kg)	Comor-bidity	DR-TB cate-gory	DR-TB regiment	Clinical information	Period of death	Cause of death	QT interval during therapy	Supporting data
27	Male/67	52	-	MDR	Lfx/Bdq/ Cfz/Eto/H/ Z/E	Discontinuation for 1 week on day 4 of therapy due to prolongation of the QT interval. The BDQ then was continued, Cfz was replaced with Cs. On M2, subject experiencing hypokalemia, but the QT interval is not prolonged. At that time, the hypokalemia was corrected.	2 weeks after the last visit for monitoring on M2.	Unknown	On M2: QTcF: 446 ms ∆QTcF: 28,26 No subsequent ECG data.	Serum Kalium (mEq/L): M2: 2,74 eGFR: M2:66 ml/min
83	Female/22	30	-	MDR	Lfx/Bdq/ Cfz/Cs/ Dlm	Discontinuation for 1 week on M1 and M4 due to QT interval prolongation and extreme tachycardia (130 beats per minute). On M5, BDQ was discontinued.	M7	Unknown	QTcF (ms): - W2: 395,42 - M1: 505,36 - M2: 436,76 - M4: 400,36 ∆QTcF (ms): - W2: 19,93 - M1: 61,27 - M2: 29,89 - M4:24,87 No subsequent ECG data.	Serum kalium (mEq/L): - M1: 4,4 - M2: 5,2 - M4: 4,3 eGFR: M6: 98 ml/min
93	Female/33	33	-	MDR	Lfx/Bdq/ Cfz/Cs/ Eto	Patients with a history of hydro-pneumothorax prior treatment. On M2, the subject was experiencing an asymtomatic prolongation of the QT interval (QTcB 582 ms) and T inversion in V2 – V5. BDQ treatment was discontinued, but the patient did not come for control a week after the discontinuation.	M3	Unknown	On M2: QTcF: 436,76 ms ∆QTcF: 83,98 ms No subsequent ECG data.	(-)

D: day 2; W: week; M: month; DM: Diabetes mellitus; DR-TB: Drug Resistant Tuberculosis; MDR: Multi-Drug resistant, XDR: Extensively Drug Resistant; BDQ: Bedaquiline; B6: Pyridoxine; Lfx: levofloxacin; Mfx: moxifloxacin; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; Eto: Ethionamide; E: Ethambutol; H: Isoniazid; Z: Pyrazinamide; QTcB: interval QT correction using Bazett's formula; QTcF: interval QT correction using Fridericia's formula; ∆QTcF: the difference of QTcF after treatment compared with baseline; ms: milli second; ml/min: millilitre/minute; eGFR: estimation of Glomerular Filtration Rate; mEQ: milli equivalent.

Cohort Prospective Study to Evaluate Immunogenicity of Epodion® (Biosimilar Epoetin-α) in Anemia Associated with Chronic Kidney Disease (CKD) Patients

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ABSTRACT

Background: *Anemia due to chronic kidney disease (CKD) is often associated with decreased erythropoietin (EPO) levels in the blood. Treatments available are improving blood iron levels and administration of exogenous EPO (rhEPO). This study aims to assess the safety and immunogenicity of Epodion, a biosimilar rhEPO product, in haemodialysis patients with CKD-associated anaemia in three Indonesian hospitals.* ***Methods:*** *This prospective, open label, single arm, and multicenter study enrolled patients with anemia associated with CKD under hemodialysis treatment. Patient eligibility was assessed within the 4-week screening period. Blood samples for determination of erythropoietin antibody (Anti-Drug Antibody) were taken at week-0, 24, and 52 using a validated and highly sensitive bridging ELISA method. Evaluation of Neutralizing Antibody (NAb) was carried out to confirm the impact of the antibody to pharmacological activity (e.g., antibody-mediated PRCA) when the ADA detection of patients was positive after screening and confirmatory assay.* ***Results****: Results from all tested patients show that Epodion could maintain hemoglobin and hematocrit levels. ADA detection using ELISA assay yielded negative results for all plasma samples of week-24 and week-52, so the evaluation of NAb was not carried out. No adverse events were considered relevant to tested product.* ***Conclusion:*** *This study proves no immunogenic effect of Epodion on stimulating immune system's antibodies in Indonesian patients with CKD-associated anemia.*

Keywords*: Anemia, anti-drug antibody, anti-rhEPO, chronic kidney disease, erythropoietin, Indonesia.*

INTRODUCTION

Chronic Kidney Disease (CKD) is clinically defined as kidney damage and/or decreased Glomerular Filtration Rate (GFR) for a minimum of three months.[1] CKD is a comorbidity of diabetes and hypertension and can indirectly increase the mortality risk of patients with cardiovascular disease, diabetes, hypertension, HIV positive, and malaria.[2] Globally, 1.2 million deaths recorded in 2015 are directly correlated with a decrease in glomerular filtration ability.[3] In Indonesia, 0.2% of the adult population were diagnosed with CKD in 2013, making it the second-largest disease in respect to the fund allocated by the national social insurance scheme.[4] A complication of CKD is anemia, which is often associated with decreased levels of erythropoietin (EPO), an endogenous hormone

responsible for inducing Red Blood Cells (RBCs) production in the bone marrow. This condition resulted from the damage of the kidney's cell mass responsible for EPO production. The standard treatment of anemia caused by CKD is the administration of exogenous EPO and improved blood iron levels.

Exogenous EPO has been developed on an industrial scale using recombinant technology (recombinant human EPO-rhEPO) to meet the market demand. Several rhEPO products that have been globally successful include Epoetin alpha manufactured by Amgen Inc., Procrit by Amgen Inc., and Eprex by Janssen Pharmaceuticals.[5] In Indonesia, several rhEPO products are developed by Indonesian and international pharmaceutical companies with marketing licenses, i.e., Epodion, Epoglobin, Epotrex, Hemapo, Rinofer, and Recormon. These products are categorized as biosimilar products, i.e., products with the same efficacy profiles, safety, and quality as those biological products approved by the Indonesian drug safety regulatory authority (BPOM) through their regulation number 17 year 2015.

As biological products with high levels of variation, the consistency between batches of production is a challenge in the manufacturing process. Insignificant differences or very small changes in production, transportation, or storage can change biological products' safety and efficacy profile. In addition, biosimilar products synthesized to resemble hormones can be recognized as foreign material by the human body and trigger immune response or immunogenicity.[6]

Indonesian government adopts WHO regulations[7] on evaluating biosimilar products. To obtain a marketing permit, pharmaceutical companies need to conduct a standard immunogenicity assessment[6,8] to ensure that the biosimilar product has similar efficacy and safety as the originator. Therefore, this study aims to assess the safety (i.e., side effects, adverse events, and serious adverse events) and immunogenicity of Epodion in hemodialysis patients with anemia associated with chronic kidney disease (CKD) within 52 weeks of the treatment period. Up to our knowledge, there have been no similar studies on CKD patients conducted in one year in Indonesia so far. The results of this study will give novel and valuable information on the safety aspect of Epodion as a biosimilar product derived from the hormone that can be used for anemia management in CKD patients.

METHODS

This study was an observational study that did not change the treatment regimen and routine received by the subject. The patients' dosage of Epodion was adjusted to the standard administration used as a routine procedure in each hospital using subcutaneous injection.

Patient eligibility was assessed within a 4-week screening period. Blood samples for determination of erythropoietin antibody (Anti-Drug Antibody) were taken at week-0, 24, and 52. Anti-Drug Antibody (ADA) was detected using a validated and highly sensitive bridging ELISA method carried out in Biotechnology Research Center Laboratory of University of Indonesia, Depok (UI Biotechnology Laboratory). Evaluation of NAb (Neutralizing Antibody) using the cell-based assay method was done to confirm the impact of the antibody on pharmacological activity (e.g., antibody-mediated PRCA) when the ADA detection of patients was positive after screening and confirmatory assay.

The Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, has reviewed the study protocol and issued the ethical clearance number: KET-1055/UN2. F1/ETIK/PPM.00.02/2019 on September 30, 2019. This ethical clearance was extended until September 29, 2021. The study was conducted according to the ethical principles set forth in the Declaration of Helsinki and carried out in accordance with the Good Clinical Practice (GCP) ICH E6 (R2) standards.

Product Information

Epodion is an alpha rhEPO product produced locally in Indonesia by PT. Daewoong Infion. This product is used in conjunction with other clinical treatments for anemic patients due to chronic kidney failure or chemotherapy. Yellowish transparent Epodion injection solution can be

injected intravenously (IV) or subcutaneously (SC). There are four Epodion products with different EPO content, i.e., 2000 IU, 3000 IU, 4000 IU, and 10000 IU.

Selection of Trial Subjects

The study was done at three Indonesian hospitals in Jakarta (Indonesia's capital) and Tangerang city, i.e., RSPAD Gatot Soebroto Jakarta, RS Pelni Jakarta, and RS Medika Tangerang from September 2019 to November 2020. Based on the prior feasibility study and calculation of precision analysis[9], 200 samples are considered a sufficient amount to represent the general population. Using this number of samples, 6.9% precision (margin of error) at 95% CI could be achieved and considered acceptable.

There are several patients' inclusion criteria, i.e., patients with anemia associated with CKD under hemodialysis treatment; male or female patients aged ≥18 years; patients with mean screening Hb concentration of ≤10 g/dL; patients on stable, adequate dialysis for at least three months (defined as no clinically relevant changes of hemodialysis regimen and/or 23/42 ©EMEA 2007 dialyzer); have used Epodion treatment at least in the past month; hemodialysis patients who are likely to remain on Epodion treatment for 52 weeks; and signed a written consent form.

Patient eligibility was assessed before the study began following the inclusion criteria. Only subjects that passed those criteria were included in the study. A consent form with detailed information about the nature, risks, and scope of the clinical trial and the expected desirable and adverse effects of the drug has been obtained before the screening began. Subjects were given enough time to freely consider their participation in this study before signing the form. Only after signing and fulfilling the inclusion and exclusion criteria, the subject could participate in the study.

Administration of Epodion

At the initial administration, patients were given Epodion dose of 50 units/kg body weight three times/week which can be done intravenously or subcutaneously. If needed, the dose can be increased to 75 units/ kg at four-week intervals from the initial administration. If the hemoglobin level increased by more than 2 g/dL after the initial dose, the administration of Epodion must be reduced to twice a week. Repair doses can be continued until the patient's hemoglobin level becomes 10 g/dL. Managed anemia condition can be maintained by administering doses between 25 to 50 units/ kg, two or three times/week. The expected hemoglobin range for treatment is 10-12 g/dL. The initial hemoglobin level and the patient's age determine the treatment dose. The maximum administration of Epodion should not exceed 200 units/kg and not more than three times/ week. During treatment, the patient's iron level was also controlled. In chronic kidney failure patients who did not undergo hemodialysis, a dose of 70-150 units/kg per week was proven to maintain 36-38% hematocrit levels for more than six months.

Endpoints

The primary endpoints were the incidence of Anti-Erythropoietin Antibodies (ADA) formation at week 52nd and the detection of Neutralizing Antibodies (NAb). The patient's plasma was used to evaluate the immune response by detecting ADA (Anti-Drug Antibody) using a validated and highly sensitive bridging ELISA method in UI Biotechnology Laboratory. The plasma was prepared based on the regular hospital procedure, i.e., blood samples were centrifuged, plasma samples were labelled and stored as aliquots at -20°C. These plasma samples were then subjected to evaluation analysis of NAb using the cell-based assay method. The Nab was carried out when the ADA detection of patients was positive after screening and confirmatory assay.

The secondary endpoints for this study were any adverse event, the incidence of ADA formation at week-24, and a comparison of the incidence of ADA formation at week-24 and week-52. Adverse Event (AE) defined in this study is any untoward event occurring in the patient after any dose of Epodion was administered. Two types of AE were used, i.e., Serious AE (SAE) and non-serious AE. SAE is defined as AE which result in death, is life-threatening, requires inpatient or prolonged hospitalization, and results in persistent or

significant disability/incapacity. Any occurring AE was assessed for its type, start date, end date, the severity of the symptoms, relevance to the test drug, measures related to the test drug, treatment, results, and significance and recorded in case report form (CRF). Any SAE that occurred was reported no later than 24 hours to the sponsor, three calendar days to the Ethics Committee, and seven calendar days to the head of the national agency of drug and food control (BPOM).

Statistical Analysis

The incidence of ADA, NAb, and AE was analyzed with descriptive statistics and displayed in frequency and percentage. A comparative analysis to compare the incidence of ADA and Nab at week 24 and week 52 were done using paired T-test with an alternative Wilcoxon Test at 95% CI and significance of $P < 0.05$.

RESULTS

Demographic Data

In this observational study, all data collected from three different sites were included (**Table 1**). Of the 200 subjects, 110 males and 90 females participated in this study with age ranging between 21 and 79 years old (average age 53 years old). Their average body weight when screening was 60.3 kg. Hematological tests, which consist of hemoglobin and hematocrit concentration, were also determined before blood sampling was performed. The average Hb and Hct concentrations were 8.5 g/dL and 27.2%, respectively. Vital sign measurement was also included at the screening period as baseline demographic data. Mean blood pressure and pulse rate were 147/77 mmHg and 79.2 bpm, respectively.

During the study period, several subjects dropped out for several reasons. By the week-24, 155 subjects (77.5%) remained, and 45 subjects (22.5%) dropped out (11 from RSPAD Gatot Soebroto, 9 from RS Pelni, 25 from RS Medika BSD). After 52 weeks of study, there were only 130 subjects (65%) remaining, and 25 subjects (12.5%) dropped out (9 from RSPAD Gatot Soebroto, 9 from RS Pelni, 7 from RS Medika BSD). Most subjects (31.5%) who did not complete the observation were due to passing away since those enrolled subjects' condition was already vulnerable. Other subjects could not complete the observation due to safety reasons (1.5%), i.e., two subjects were infected by COVID-19, and a subject had kidney improvement. Besides that, patient withdrawal (1.5%) was due to moving to another hospital. However, based on the observation of the principal investigator in this study, there is no SAE and AE related to the test product in all cases.

Table 1. Baseline demographic and characteristic of study subjects.

Baseline Demographic Data	RSPAD Gatot Soebroto (n= 50)		RS PELNI (n=58)		RS Medika BSD (n=92)		Total (n=200)	
	N		n		N		n	
Gender (%)								
- Male	27		32		51		110	
- Female	23		26		41		90	
	Mean	range	Mean	range	Mean	range	Mean	range
Age (years)	52	21-74	53	21-79	53	22-78	53	21-79
Body weight (kg)	64.3	37.0-113.3	62.7	41.0-89.0	57	29.8-96.2	60.3	29.8-113.3
Body height (cm)	161.5	142-184	160.4	140-173	-	-	160.9	140-184
Hematological Test								
- Hb (g/dL)	8.9	7.0-10.4	8.1	5.6-10.0	8.6	6.7-11.5	8.5	5.6-11.5
- Hct (%)	26.9	21-33	24.3	21.0-29.0	27.6	20.2-36.8	27.2	20.2-36.8
Vital Sign								
- Systole (mmHg)	156	100-201	148.7	99-199	140.8	81-193	147	81-201
- Diastole (mmHg)	83	43-120	75.1	55-102	75.1	36-102	77	36-120
- Pulse rate (bpm)	82	63-120	80.1	56-102	77.3	45-131	79.2	45-131

Mean of Hb, Hct, systolic and diastolic blood pressure, also pulse rate were similar and there were no clinically significant changes from week-0 to week-52 (**Figure 1, Table 2**). There was also no significant difference between value of week-0 and week-24. These shows that Epodion could maintain the hemoglobin and hematocrit levels of patients tested.

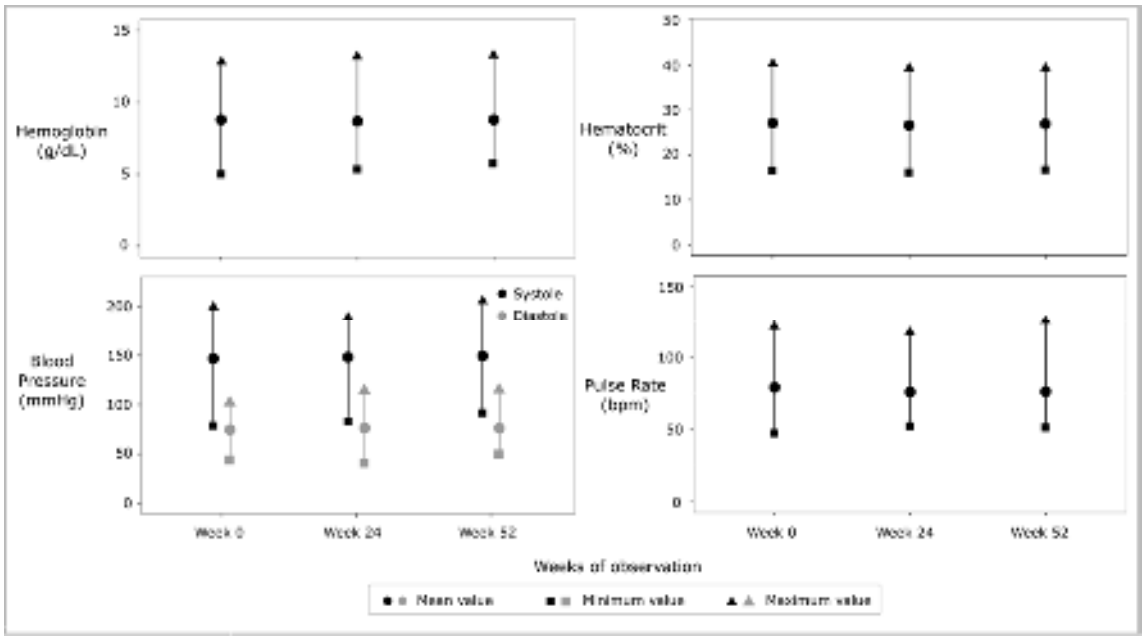

Figure 1. Measured hematological and vital signs during the treatment period.

Table 2. Paired T-test results between weeks of measurement on measured hematological and vital signs during the treatment period.

Parameters measured	Paired T-test results			
	Week 0-24		Week 0-52	
	p-value	Sig.	p-value	Sig.
Hematological Test				
- Mean Hb (g/dL)	0.256	NS	0.991	NS
- Mean Hct (%)	0.056	NS	0.828	NS
Vital Sign				
- Systole (mmHg)	0.435	NS	0.25	NS
- Diastole (mmHg)	0.076	NS	0.192	NS
- Pulse rate (bpm)	0.052	NS	0.103	NS

Primary Endpoints

After 52 weeks of treatment, there were no cases of positive Anti-Erythropoietin Antibodies (ADA) reported (Table 3). Nevertheless, the incidence rate of false positive results of ADA-screening from plasma samples of week-52 was 3.1% (**Table** 3). However, after confirmatory assay, all results become negative. Since there was no ADA detected in the plasma samples, further investigation to evaluate the neutralizing effect of the detected ADA using cell-based assay method to confirm the impact of the antibody to pharmacological activity (such as antibody mediated PRCA) was not required.

Secondary Endpoints

During the treatment period, one or more AEs were experienced by 51% (102/200) of subjects (T**able 4**). Serious AEs were experienced by 41.5% (83/200), with 63 subjects died during the treatment period. However, the observation by

Table 3. Summary results of immunoassay data.

	Week-24 N	%	Week-52 N	%
Total sample	158		130	
Negative ADA	155		126	
Positive ADA	0		0	
Likely false positive ADA	3	1.9	4	3.1
- re-analysis	3		4	
- final result negative	3		4	
- final result positive	0		0	
Total : Negative ADA	158		130	
Positive ADA	0		0	
NAb done	0		0	

the principal investigators in this study concludes that no deaths were considered relevant with the administered Epodion (Appendix 1). Of the 102 subjects who experienced AEs (Table 4), 189 adverse events occurred during a year treatment period (Table 5, Appendix 1). From 189 adverse events reported, the most frequent of adverse events was transfusion (28% of AE) occurred in 18 subjects, followed by hospitalization with unknown specific reason (19% of AE), and COVID-19 (4.8% of AE).

SAE cases that occurred during the study have been reported to the Ethic Committee. Subjects who suffered from SAE and required hospital admission were largely due to sepsis, pneumonia, COVID-19, and anemia. Similar to the incidence of ADA formation at week-52, all the results of week-24 were negative, with an incidence rate of false positive result was 1.9%. Thus, there was no data to compare between week-24 and week-52.

Table 4. Subject with adverse events.

Subjects with Adverse Events (AE)	RSPAD Gatot Soebroto (N = 50)		RS PELNI (N = 58)		RS Medika BSD (N = 92)		Total (N = 200, safety population)	
	N	%	n	%	N	%	n	%
Serious AE	23	46	21	36.2	39	42.4	83	41.5
Non-serious AE	9	18	20	34.5	1	1.1	30	15
All	**26**	**52**	**37**	**63.8**	**39**	**42.4**	**102**	51

Note: All data indicates the number of all patients experiencing Serious and/or Non-serious adverse events; one patient can experience both events

Table 5. Adverse events.

Adverse Events (AE) occured	RSPAD Gatot Soebroto (N = 50)		RS PELNI (N = 58)		RS Medika BSD (N = 92)		Total (N = 200, safety population)	
	N	%	n	%	n	%	n	%
Serious AE	31	36	31	16.7	52	49.1	114	30.2
Non-serious AE	12	14	62	33.3	1	0.9	75	19.8
All	43	50	93	50	53	50	189	50
Total	86	100	186	100	106	100	378	100

Note: All data indicates the number of all patients experiencing Serious and/or Non-serious Adverse Events; one patient can experience both events

Data Analysis

Antibody detection using ELISA assay showed negative results for all plasma samples of week-24 and week-52, even though some were detected as likely false positives before the confirmatory assay was performed. Therefore, the significance of data between week-24 and week-52 was not analyzed further.

DISCUSSION

Epodion is a biological product that is considered biosimilar to the original reference product (Eprex®); hence, evaluating its immunogenicity is crucial. Most biological products can induce unwanted immune reactions due to the formation of antibodies, which then contribute to potential adverse effects.[10] This immunogenic effect can impact the loss of efficacy of the therapeutic product.[11] Up to the moment this study was done, Epodion has been proven to successfully and safely treat anemia in patients with CKD. Patients receiving Epodion treatment showed a stable and maintained hemoglobin level.

The high AE observed is possibly related to the initial patient condition. Most of the patients recruited were elderly (mean age 53 years; see **Table 1**) with a considerably vulnerable condition of low Hb levels and underlying conditions, such as hypertension. Most AE incidence reported were blood transfusion to raise the patients' Hb level. Epodion treatment was meant to maintain their Hb level, which proved to be successful after weeks of observation. However, in most patients, their Hb was still considered low. A meta-analysis study[12] mentioned that a higher Hb target to patients with anemia caused by CKD using rhEPO might increase the risk of death. Therefore, in this study, treatments used were a combination between transfusion and a controlled dose of rhEPO Epodion.

The studied subjects did not develop antibodies on anti-epoetin, a result similar to other studies in European hospitals.[13,14] Another Indonesian study using biosimilar rhEPO products Renogen and biosimilar rhEPO origin Eprex[15] also showed similar findings. The efficacy and safety of biosimilar rhEPO on treating CKD-associated anemia were also shown in another study with pre-dialysis patients.[16]

The patient who develops an antibody to rhEPO can become severely anemic and requires frequent RBCs transfusions. These antibodies recognized the core protein of endogenous erythropoietin after complete deglycosylation of the molecule. The high-affinity binding sites also bound denatured erythropoietin, suggesting that these antibodies are directed against a linear epitope of the erythropoietin molecule. The level of immunoprecipitation antibodies was able to neutralize very high amounts of erythropoietin receptors. Thus, these antibodies can neutralize all erythropoietin molecules produced by the patients, fully inhibiting erythropoiesis.[17]

Based on the EMA guidelines, several factors may influence the immunogenicity of therapeutic proteins, e.g., patient-related factors, disease, or product itself. Immunogenicity data are highly dependent on the types of assays used. From different types of assays used to detect anti-Erythropoietin antibodies, the most reliable results is provided by ELISA assay. The bridging ELISA assay in this study is preferred for its sensitivity, specificity, and convenience for managing large numbers of serum samples.[18]

The analysis of plasma samples of 200 patients with CKD-associated anemia collected from three different hospitals showed the presence of anti-Erythropoietin antibodies from those samples. A screening assay should be capable of detecting antibodies (ADA) induced against the Epodion. Nevertheless, the detection of some false-positive results is inevitable since an absolute screening-assay specificity is normally unattainable (EMEA, 2007). These false-positive results were necessary to be confirmed through confirmatory assay. All of them were considered eliminated and showed negative results after the confirmatory assay was performed. There were no patients developing non-neutralizing or neutralizing anti-epoetin antibodies or pure red cells aplasia (PRCA). Therefore, determination of the neutralizing activity was not necessary. The data reflect that all patients using Epodion in a year were considered negative for antibody to Epodion in an ELISA assay and continuation of Epodion therapy will be possible.

This study has limitations. The data gathered

only covers a particular area of Indonesia, which did not fully represent the ethnic diversity of Indonesian people. Patients' characteristics such as ethnicity, nutritional status, and age can largely affect the prognosis and timing of AE happened in CKD patients.[19] These characteristics can act as confounding factors that may affect the parameters measured. Even though we did include quite extensive inclusion and exclusion criteria, it is quite difficult to obtain a wide array of subjects. Most subjects in this study were already in an initial vulnerable condition. Some of them did not follow the international treatment standard of three times per week hemodialysis. Nevertheless, the investigators in this study follow the standardized protocols of patient evaluation to obtain valid data.

CONCLUSION

This study proves that Epodion is considered safe and did not induce immunogenetic reaction in considered doses in patients from three Indonesian hospitals during one year of observation. These results also indicate that the administration of Epodion did not show any symptoms related to PRCA. However, this study also implies that the initial condition of patients plays a vital role in determining the potential adverse effect that might happen. Therefore, prospective future studies should include a wide array of patients in a less vulnerable condition. Datasets should cover patients from other Indonesian provinces since differences in patients' ethnicity, and nutritional diets may be confounding variables. Other recommended future studies may also involve EPO-naive patients, administration of EPO dose per body weight, and standardization of patients' hemodialysis frequency three times/ week according to international standards.

CONFLICT OF INTEREST

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Effect of Cholecalciferol Supplementation on Disease Activity and Quality of Life of Systemic Lupus Erythematosus Patients: A Randomized Clinical Trial Study

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ABSTRACT

***Background**: Increase in the prevalence and survival rates has led to the assessment of disease activity and quality of life of SLE patients as targets in treatment. Cholecalciferol was considered as having a role in reducing disease activity and improving quality of life. **Methods**: A double blind, randomized, controlled trial was conducted on female outpatients aged 18-60 years with SLE, consecutively recruited from September to December 2021 at Cipto Mangunkusumo Hospital. Sixty subjects who met the research criteria were randomized and equally assigned into the cholecalciferol and placebo groups. The study outcomes were measured at baseline and after 12 weeks of intervention. **Results**: Out of 60 subjects, 27 subjects in cholecalciferol group and 25 subjects in placebo group completed the intervention. There was a significant improvement on the level of vitamin D (ng/ml) after intervention in the cholecalciferol group, from an average of 15,69 ng/ml (8.1-28.2) to 49,90 ng/ml (26-72.1), and for the placebo group from 15,0 ng/ml (8.1-25,0) to 17.35 ng/ml (8.1-48.3) (p<0,000). Results of the MEX-SLEDAI score showed significant differences in both groups after the intervention, with a significant decrease in the cholecalciferol group from 2,67 (0-11) to 1,37 (0-6), compared to the placebo group from 2,6 (0-6) to 2,48 (0-6) (p<0,001). There were no significant differences on the quality of life in both groups. **Conclusion**: Supplementation of cholecalciferol 5000 IU/day for 12 weeks was statistically significant in increasing vitamin D levels and improving disease activity, but did not significantly improve the quality of life of SLE patients.*

***Keywords**: cholecalciferol, disease activity, quality of life, systemic lupus erythematosus.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by autoantibody deposits in tissues, organ damage and various clinical manifestations. SLE is better known as a syndrome than a single disease and the course of SLE is still unpredictable; it can persist, recure, or recover.[1]

The diagnosis and therapy of SLE had improved and made a significant impact on increasing the survival rate of SLE patients.[2] By increasing the survival rate, the target of treatment is not only to control disease activity and prevent organ damage but also to pay attention to the patient's quality of life.[3]

Vitamin D deficiency has a role in the pathogenesis of SLE, especially in the regulation of growth, proliferation, apoptosis, and immune system function. Low vitamin D is associated with decreased Regulatory T-cells (Tregs), which function to increase tolerance to self-antigens. In addition, it also increases the auto reactive activation of B cells to produce autoantibodies, increases the activation and proliferation of Th1 helper cells and produces Interferon-alpha (IFN-α) through plasmatocytoid Dendritic Cells (pDC), producing an excess of pro inflammatory cytokines through macrophages. This process forms immune complexes, which leads to tissue damage and continuous release of self-antigens.[4,5] In vitro studies have shown that 1,25 dihydroxy vitamin D can inhibit the differentiation of Dendritic Cells (DCs), T cell proliferation, cytokine production, activated B cell proliferation and plasma cell formation.[5,6] The relationship between vitamin D and SLE is complex since SLE can cause low levels of vitamin D and vitamin D deficiency further plays a role in the etiology and worsening of SLE symptoms.[6,7] However, the relationship between vitamin D levels and SLE disease activity has been reported to be inconsistent and is still debated.[8] Several studies have shown that vitamin D is associated with SLE disease activity through several mechanisms; meanwhile, other studies have reported that there was no relationship between vitamin D levels and SLE.

Effect of vitamin D supplementation on SLE disease activity is still controversial, and its role on the quality of life of Indonesian SLE patients has never been studied. As a result, this study aims to examine the benefits of vitamin D supplementation on disease activity and quality of life of SLE patients in Indonesia.

METHODS

This study is a double blind randomized controlled trial. Subjects were allocated in each treatment arm using permuted block randomization, with a block size of four and concealed code lists. Investigators, doctors, and subjects were blinded to treatment allocation (double blind).

Study Participants

Women with systemic lupus erythematosus aged 18-60 years old with hypovitaminosis D as inclusion criteria. Exclusion criteria included declining consent to participate, late stage chronic kidney disease (staged 4-5), decompensated liver cirrhosis, consumption of glucocorticoids (equivalent to prednisone 20 mg/day) in the past 30 days, pregnant or lactating, patients with acute infection, hypercalcemic patients, anticonvulsant consumption. Dropout criteria included unwillingness to continue participation in the study, compliance rate <70% for both arms, side effects to vitamin D such as nausea, vomiting, diarrhea, cramps that could not be controlled with medication, hospitalized due to infection, changes in the regiment or dose of immunosuppressant or glucocorticoids (equivalent to prednisone 20 mg/day) during the trial. Subjects were consecutively recruited from September 2021 to December 2021 at Allergy and Immunology Outpatient clinic in Cipto Mangunkusumo Hospital, Jakarta.

Intervention Protocol

After providing written consent, eligible subjects were randomly assigned to either the cholecalciferol (Prove D3 1x5000 IU) or placebo (Saccharum lactis 1x5000 IU) arm. Both the cholecalciferol and placebo tablets were indistinguishable by appearance.

The allocated treatment was dispensed to the subjects every four weeks. The collected data consisted of subjects' demographic data

(age, income, level, duration of illness, Body Mass Index, organ involvement, treatment, comorbidities, initial methylprednisolone dose, initial MEX-SLEDAI score), clinical data (level of hemoglobin, white blood cell, platelets, Erythrocyte Sedimentation Rate, Creatine Kinase (CK), estimated Glomerular Filtration Rate (eGFR), micro-albuminuria, anti-dsDNA, vitamin D levels, blood calcium levels). Quality of life was assessed using the lupus quality of life (Lupus QoL) questionnaire with a 5-point Likert scale.

Measurement of study outcomes was conducted at baseline and after 12 weeks of intervention. Levels of vitamin D were measured using the ELISA kit, and disease activity was measured using the MEX-SLEDAI score, with a score ranging from 0 to 34. Quality of life was assessed using the Lupus Quality of Life (Lupus QoL) questionnaire with a 5-point Likert scale ranging from 0 to 100. All variables were measured initially and 12 weeks after intervention. Adverse events, side effects, and compliance rates were evaluated every four weeks.

Sample Size

The minimum sample size required to assess disease activity of SLE was 10 subjects in each treatment arm. A minimal sample to assess the quality of life was not determined due to the novel nature of the study. Total number of subjects in each treatment group was 30 subjects.

Ethics

This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia / Cipto Mangunkusumo Hospital (No. KET-745/UN2F1/ETIK/PPM.00.02/2021). The study procedure was performed in accordance with the Declaration of Helsinki. This study has been registered in clinicaltrial.gov (Registered no. NCT05326841).

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20. Dropout subjects were excluded from the analyses (per-protocol analysis). Mean and standard deviation values were calculated for normally distributed numerical data. Calculation of median and interquartile range values was performed for numeric data with non-normal distributions. Unpaired independent T tests were performed to analyze the changes in the variables between the vitamin D (*Prove D3*) group and placebo when the data distribution was normal. In cases of non-normal data distribution, Mann-Whitney tests were performed.

RESULTS

Despite recruiting 70 SLE subjects to participate in the study, as many as 10 subjects were excluded from this clinical trial, based on the research criteria, which resulted in 60 subjects who were randomized and equally assigned into cholecalciferol (*Prove D3*) and placebo groups. A total of 27 subjects in the cholecalciferol group and 25 subjects in the placebo group had completed the intervention trial (**Figure 1**).

From 27 subjects who completed the intervention in the cholecalciferol group, the mean age was 32,9 (20-40) years old, and most (60%) had an education level of up to senior high school. Eighteen subjects (40%) had a duration of disease greater than 5 years. Most subjects (30%) weighed within normal ranges of BMI. In the placebo group, the mean age was 29.5 (19-49) years old, with a majority (56.7%) having middle school education level. A plurality (46.7%) of subjects in this group had a duration of disease greater than 5 years, and normal weight was observed in 13 subjects (43.3%).

In the cholecalciferol group, mucocutaneous organ involvement was found in all subjects, followed by musculoskeletal involvement in 29 subjects (96.7%). Hydroxychloroquine (HCQ) was the most commonly prescribed treatment, given to 21 subjects (70%), followed by Myfortic (63.3%) and Imuran (23.3%). Most patients had at least one comorbidity with 5 subjects (31.3%) having only one. In the placebo group, mucocutaneous involvement was present in 29 subjects (96.7) followed by musculoskeletal involvement in 25 subjects (83.3%). Treatment by HCQ was standard for 23 subjects (76.7%), followed by myfortic in 17 subjects (56.7%) and imuran in 3 subjects (10%). Ten subjects (33.3%) had one comorbidity, with most having more than one. Results of the demographic characteristics are summarised in **Table 1**.

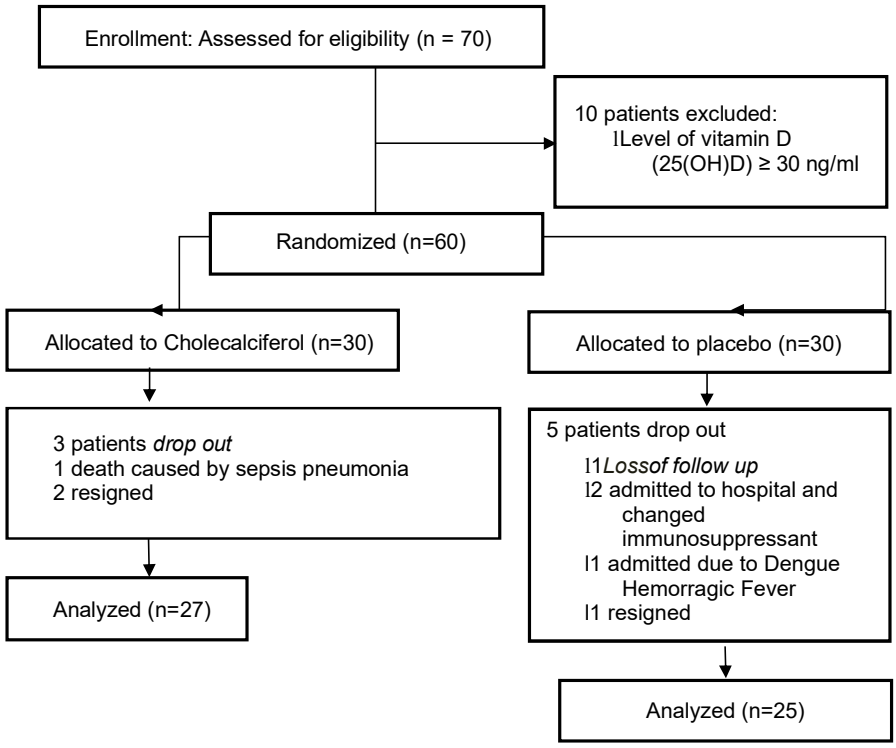

Figure 1. Flow diagram of randomized control trial.

Table 1. Characteristic study subjects.

Variables	Intervention (n=30)	Placebo (n=30)
Age (year), median (IQR)	32.9 (20-46)	29.5 (19-49)
Level of education, n (%)		
Low	3 (10.0)	3 (10.0)
Middle	18 (60.0)	17 (56.7)
High	9 (30.0)	10 (33.3)
Income, n (%)		
<UMR	16 (53.3)	19 (63.7)
>UMR	14 (46.7)	11 (37.3)
Disease of duration, n (%)		
<1 year	6 (20.0)	7 (23.3)
1-5 year	6 (20.0)	9 (30.0)
>5 year	18 (40.0)	14 (46.7)
IMT, n (%)		
Underweight	6 (20.0)	4 (13.3)
Normoweight	9 (30.0)	13 (43.3)
Overweight	8 (26.7)	8 (26.7)
Obesity	7 (23.3)	5 (16.7)
Organ involvement, n (%)		
Mucocutaneous	30 (100)	29 (96.7)
Musculosceletal	29 (96.7)	25 (83.3)
Renal	18 (40.0)	10 (33.3)
Hematology	15 (50.0)	8 (26.7)
Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)	1 (3.3)	2 (6.7)
Serositis	2 (6.7)	0
Treatment, n(%)		
Hydroxyichloroquine (HCQ)	21 (70.0)	23 (76.7)

Myfortic	19 (63.3)	17 (56.7)
Imuran	7 (23.3)	3 (10.0)
Methotrexate (MTX)	0	1 (3.3)
Comorbidity, n (%)		
None	3 (18.8)	11 (36.7)
One	5 (31.3)	10 (33.3)
Two	3 (18.8)	4 (13.3)
Three	2 (12.5)	4 (13.3)
Four	2 (12.5)	3 (3.3)
Five	1 (6.3)	0 (0.0)
Initial dose of methylprednisolone mg/day, median (IQR)	3.53 (0-16)	5.13 (0-16)
Initial MEX-SLEDAI score, median (IQR)	2.67 (0-11)	2.6(0-6)

IQR: Interquartile Range ; n= total subjects

Quality of life in the two groups had similar median values across the 8 domains. In the physical health domain, the average cholecalciferol group score was 79.6 (50-100), which was slightly higher than the average placebo group, which was 79.0 (21-100). Pain scores in the cholecalciferol group (median 73.3 [33-100]) were on average lower than the placebo group (median 78.5 [25-100]). On average, the planning score in the cholecalciferol group was 79.1 (25-100), which was lower than the placebo group score of 84.4 (25-100). The median intercourse score in the cholecalciferol group was 86.2 (12.5-100), which was higher than the placebo group (median 81.4 [0-100]). Emotional health scores in the cholecalciferol group (median 65.4 [8-95]) were lower than the placebo group (median 75.4 [25-100]), and median self-image scores in both groups were 66.4 (15-100) and 77.1 (15-100) for the cholecalciferol and placebo arm respectively. Fatigue score in the intervention group (median 57.7 [12.5-93]) was lower on average, compared to the placebo group (median 70.2 [18-100]). Quality of life scores is summarised in **Table 2**.

The initial levels of vitamin D 25 (OH) in the two groups before intervention were similar. After an intervention, the cholecalciferol group had an increase of average vitamin D 25(OH) levels from 15.69 ng/ml (8.1-28.2) to 49.90 ng/ml (26-72.1), resulting in an average increase of 33.8 ng/ml. In the placebo group, average vitamin D levels also increased slightly by 2.5ng/ml from 15.0 ng/ml (8.1-25,0) to 17.35 ng/ml (8.1-48.3). The difference in the increase in average vitamin D 25(OH) levels between the two groups was statistically significant ($p<0.000$). Results of initial laboratory values and analysis of vitamin D changes are summarised in **Table 3** and **Table 4**, respectively.

The effect of giving cholecalciferol on SLE disease activity, based on the MEX-SLEDAI results, showed a significant difference between the cholecalciferol group and the placebo group. An average decrease in the MEX-SLEDAI value of about 1.29 in the intervention group was observed, compared to the average decrease of 0.12 in the MEX-SLEDAI value of the placebo group. This indicates that the intervention with cholecalciferol provided an improvement, in the

Table 2. Characteristic initial quality of life.

Variables	Intervention (n=30)	Placebo (n=30)
Lupus QoL, median (IQR)		
Physical health	79.6 (50-100)	79.0(21-100)
Pain	73.3 (33-100))	78.5 (25-100)
Planning	79.1 (25-100)	84.4 (25-100)
Intimate relationship	86.2 (12.5-100))	81.4 (0-100)
Burden to others	63.0 (7-100)	72.1 (10-100)
Emotional health	65.4 (8-95)	75.4 (25-100)
Body image	66.4 (15-100)	77.1 (15-100)
Fatique	57.7 (12.5-93)	70.2(18-100)

Table 3. Initial laboratory characteristics.

Variables	Intervention (n=30)	Placebo (n=30)
Hemoglobin (g/dl), median (IQR)	11.9 (7.2-14.1)	12.0 (7.8-14.3)
White Blood Cell (/uL), median (IQR)	6639 (4100-10670)	7048 (3190-13110)
Platelets (/uL), median (IQR)	298966 (202000-396000)	320066 (139000.0-549000)
LED (mm), median (IQR)	38.1 (0-140)	41.8 (0-144)
CK (U/L), median (IQR)	66.0 (16.0-167.0)	54.7(16-178)
eGFR (ml/min/1.73m^2), median (IQR)	111 (68-140)	105.7 (12-131)
Microalbuminuria (mg/g kreatinin), median (IQR)	169 (0-2085)	118.3 (0-792)
Anti dsDNA (IU/mL), median (IQR)	266.7 (1.1-1235)	223.1 (1.9-967.0)
Initial Vitamin D (ng/ml), median (IQR)	15.69 (8.1-28.2)	15.0 (8.1-25.0)
Calsium level mg/dl, mean (SD)	9.27 (0.49)	9.40(0.30)

IQR= Rentang Interquartile; SD= Standard Deviation

Table 4. Changes in pre and post intervention vitamin D Levels.

Variables	Group [Mean (SD)]		P
	Intervention (n=30)	Placebo (n=30)	
Vitamin D (ng/ml)	33.8 (SD 12.04)	2.5 (SD 10.58)	<0.000

Unpaired T-test.

form of a decrease in SLE disease activity (p = 0.015). The analysis of the SLE disease activity post intervention is described in **Table 5**.

The effect of giving cholecalciferol compared to placebo on the Lupus Quality Of Life (Lupus Qol) scores showed that there was no significant difference in the quality of life between the two groups across all domains including physical health, pain, planning, intimate relationships, burden to others, emotional health, self-image and fatigue **(Table 6)**.

Table 5. Effect of cholecalciferol supplementation on SLE disease activity using MEX-SLEDAI.

Variable	Group [Median (IQR)]		p
	Intervention (n=30)	Placebo (n=30)	
MEX-SLEDAI	-1.29 (-5.0; 4.0)	-0.12 (-5.0; 6.0)	0.015

Table 6. Changes in the total quality of life of SLE patients pre and post intervention.

Lupus QoL	Intervention (n=30)	Placebo (n=30)	p
Total QoL Mean (SD)	21.32 (90.57)	14.4 (78.2)	0.773

DISCUSSION

In this study, the results in the vitamin D group showed a significant increase in 25(OH) D levels when compared to the placebo group. These results are in accordance with the randomized trial by Abou-Raya et al. where SLE patients receiving vitamin D 2000 IU/day and had a greater increase in post-intervention vitamin D 25(OH)D levels, compared to the placebo group. On average, the vitamin D 25(OH) level was greater by 17.9 ng/ml with a mean of 37.8±16.3 ng/ml in the intervention group, compared to 19.9±16.2 ng/ml in the placebo group ($p<0.05$).[9]

The effect of cholecalciferol supplementation on SLE disease activity, showed that there was a greater decrease in average MEX-SLEDAI values of the intervention group compared to the placebo group. The results of this study are concordant with the research by Kalim et al, where a double-blinded randomized clinical trial was conducted involving 20 SLE patients who were given vitamin D supplementation of 1200 IU/day for 3 months, compared to 19 SLE patients who received a placebo. The results of this study showed a significant decrease in the SLEDAI scores from an average of 12.65 ± 4.85 to 6.20 ± 2.67 in the vitamin D group, compared to the slight decrease in SLEDAI scores of the placebo group (10.74±2,75 to 9.68±2.26).[10]

Vitamin D plays a role in regulating Treg cells through the process of tolerogenic induction of dendritic cells, which will produce IL-10 through CD4+ T cells and Treg-specific antigens. High levels of vitamin D can stimulate the transcription factor FOXP3, which plays

a role in the formation and enhancement of Treg function. High vitamin D levels are also associated with anti-inflammatory lymphoid polarization. Tregs stimulated by vitamin D will function to control the immune response of T cells, both alloreactive or autoreactive, by producing inhibitory cytokines, namely IL-10 and TGF-beta, through the release of granzyme and perforin or expression of CTLA-4 to prevent antigen presentation or proinflammatory response. Vitamin D can increase Tregs both directly or indirectly. The results of the study showed that there was a relationship between high Treg levels and immunosuppressive phenotypes. Vitamin D supplementation can decrease SLE activity. This is due to the role of vitamin D in inhibiting Th1, Th17 and increasing Tregs and Th2. Vitamin D also decreases the differentiation and proliferation of B cells.[12]

After the intervention, there was an increase in the Lupus QoL score in the cholecalciferol and the placebo group, but the differences between the two results were not significant (p=0.773). This was due to the good baseline quality of life in both groups since both groups had a median score greater than 50 in each domain prior to intervention. In addition, several factors can affect the quality of life in this study such as age, duration of illness, level of education, disease activity. In this study, the difference in age between the two groups was not much different and on average subjects were relatively young. In addition, the duration of illness and level of education may also play a role in the quality of life since a patient with longer duration of disease may have better physical health, mental health and emotional regulation. Higher education levels on average will lead to a better quality of life. Quality of life in this study was good and not related to disease activity and organ involvement.[14]

Although there were three serious adverse events (SAEs) reported in the vitamin D group (nausea, pneumonia, iron deficiency anemia), further investigation showed that they were not related to vitamin D administration.

The advantage of this study was that it used a double-blinded randomized trial design, with a long observation time of 12 weeks. In addition, the use of cholecalciferol tablets in this study at a dose of 5000 IU was in accordance with the guidelines of the European Food Safety Authority, which recommends the use of vitamin D at a daily average of 4000 IU/day (100µg/day) for adults and the elderly with normal weights. The tablet preparations taken are also small, tasteless, and odorless, making it easier for patients to consume. This study was also successful in increasing vitamin D levels, achieving sufficient values, and succeeded in significantly improving disease activity. The study also succeeded in improving the quality of life of the subjects, albeit slightly.

The weakness of this study is a large number of tablets that have to be consumed per day and the absence of specific inflammatory marker examinations that can explain the decrease in SLE disease activity. With respect to the quality of life study, the sample size needs to be increased, and the research time needs to be longer than at least 6 months.

CONCLUSION

In this study, the results showed that daily cholecalciferol (5000 IU) supplementation for 12 weeks improved disease activity, but did not significantly improve the quality of life of SLE patients.

From this study, it can be proven that cholecalciferol (5000 IU)/day supplementation for 12 weeks increases vitamin D levels and improves disease activity in SLE patients. However, it is necessary to conduct an assessment in the form of inflammatory markers that are more specific for inflammatory conditions in the LES so that they can explain the activity of the LES. And related to the role of cholecalciferol supplementation on the quality of life of SLE patients, it is still not significant in this study, so further research is needed with a larger sample size and a longer time of at least 6 months.

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The Role of High Sensitivity C-reactive Protein to Predict Delirium Persistence in Elderly Patients with Pneumonia: A Prospective Cohort Study

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ABSTRACT

***Background**: Delirium is a disorder of acute full attention, and cognitive function commonly occurs at elderly which can prolong hospitalization, dependence rate, morbidity, and mortality, with pneumonia infection as one of its risk factors. Several markers have been studied for delirium, but relationship between delirium severity and persistence remains unclear. This study aimed to examine the role of hs-CRP, pNF-H, S100B, and NLR to predict delirium persistence.* **Methods**: A prospective cohort study was conducted among 80 subjects who were admitted to the internal ward in dr. M. Djamil Hospital in Padang. Subjects were grouped based on severity of delirium using the Memorial Delirium Assessment Scale and followed up until discharged to determine delirium persistence event.* **Results**: *Mean age of subjects is 70.7±7.4 years, 39 (48.8%) male and 41 (51.2%) female,consisting of 29 mild, 26 moderate, and 25 severe delirium. Levels of hs-CRP in mild, moderate, and severe delirium are 13.36±0.79, 13.56±0.78, and 13.88±0.59 mg/L (p=0.038), respectively. Median NLR values for mild, moderate, severe delirium were 6.80 (1.00-31.00), 9.50 (3.60-46.00), and 11.90 (2.80-46.50) (p=0.026). Cut off value hs-CRP 13.61 mg/L has significant difference for delirium persistence event (OR 2,54; 95% CI 1,01-6,39). Median levels of pNF-H and S100B are not significant in different delirium severity, regardless of non-persistent or persistent.* **Conclusion**: *Hs-CRP levels exceeding 13.61 can predict risk of persistent delirium, but not with levels pNF-H, S100B, and NLR.*

***Keywords*: *Delirium persistence, hs-CRP, elderly, pneumonia*.

INTRODUCTION

Delirium is an acute global impairment of attention and cognitive function common in old age.[1] The incidence of delirium is associated with prolonged length of stay, high mortality, and risk for cognitive impairment later in life. Delirium occurs due to the interaction between predisposing factors that determine the susceptibility of the patient and precipitating factors.[1]

Infection is one of the triggers of delirium.[2] Pneumonia is the most common infection and is the leading cause of hospitalization and death in the elderly. The incidence of delirium during hospitalization in pneumonia patients is about 31%.[3] Research shows delirium is a predictor of mortality in elderly pneumonia patients.[4] Delirium conditions can be reversible but can also persist for a longer time, known as persistent delirium. Several studies set different times as a standard for persistent delirium, one of which is at the time of discharge.[5] Cole et al. found a persistent delirium proportion of 44.7% upon

discharge.[6] Lee et al.[5] found prolonged delirium in elderly patients after hip fracture surgery 20% at four weeks.[5] This persistent condition of delirium sometimes causes confusion and misunderstanding for families.

Systemic inflammation will continue to be neuroinflammatory and cause increase in blood-brain barriers' permeability leading to damage to the synapse.[7] The severity of inflammation in infection can be assessed by various markers, including high sensitivity C-reactive protein (hs-CRP) and neutrophil-lymphocyte ratio (NLR). Systemic inflammation will continue to be neuroinflammatory and cause activation of microglia and astrocytes, which will excrete S100 Beta (S100B).[8] Mietani et al. observed elevated level of phosphorylated neurofilament heavy subunits (pNF-H), the main structures of the central axons of the nervous system levels, in 30 of the 41 patients who had non-cardiac postoperative delirium under general anesthesia.[9]

It is not yet clear whether hs-CRP, pNF-H, S100B, and NLR are associated with the persistence of delirium. This study aims to determine the role of hs-CRP, NLR, S100B, and pNF-H levels in predicting risk of persistence of delirium in elderly patients with pneumonia in the acute medical ward.

METHODS

This prospective cohort study was conducted in the acute medical ward of dr. M. Djamil Hospital from February 2021 to December 2021. Subjects were recruited after obtaining approval from ethical review board. The study sample was delirium patients aged 60 years or older with pneumonia infection. Patients who consumed antipsychotic drugs, suffered Parkinson's, acute stroke, rheumatoid arthritis, head trauma, or undergoing surgery were excluded. Eligible patients were followed up until discharge. Patients who were still delirium when discharged were classified as persistent delirium.

Ethical Approval

The Research Ethics Committee of Medical Faculty Andalas University number 227/ UN.16.2/KEP-FK/2021.

Delirium Assessment

Delirium was assessed using the Confusion Assessment Method-Intensive Care Unit instrument. Delirium was diagnosed if there is a change in mental status with acute onset or fluctuating course, inattention, disorganized thinking, or altered level of consciousness.[10] A geriatrician carried out delirium assessments. The severity of delirium was assessed with the Memorial Delirium Assessment Scale (MDAS), which has ten items with four scales and a maximum value of 30. An MDAS score of 13-16 indicates mild delirium, a score of 17-24 moderate, and severe delirium if the score >24. [11]

Specimen Collection and Methods of Analyses

A 3 ml blood sample was collected within 24 hours of hospitalization in an acute medical ward. Serum was separated within 2 hours and stored at a temperature of -80^{0}C until later analysis. Examination of hs-CRP, S100B, and pNF-H is carried out at the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas. Serum concentrations of hs-CRP, pNF-H, and S100B were measured by the Enzyme-Link Immunosorbent Assay (ELISA) by BioRad. Hs-CRP was measured using high sensitivity human ELISA kits (DBC Canada), Abbexa for pNF-H, and LSBio reagent for S100B analyzed. Each examination was carried out duplo. The NLR assessment was carried out by calculating the differential count of leukocytes at the Central Laboratory of dr. M. Djamil hospital Padang.

Statistical Analysis

Differences in hs-CRP levels at varying severity of delirium were analyzed with ANOVA, while differences in NLR values, pNF-H levels, and S100B were analyzed with the Kruskal Wallis test because the data were not normally distributed. The role of these markers in predicting persistent delirium is done by first establishing a cut-off point using the receiver operating characteristic curves. The analysis continued with multivariate logistic regression. Furthermore, the odds ratio of each marker is determined in predicting risk of persistent delirium. The odds ratio not crossing one is said to be significant.

RESULTS

Of the 170 patients initially screened for the study, 15 patients were excluded and 75 patients died before discharge. Thus, 80 patients completed the study and were included in the analysis. Thirty-two (40%) subjects were still in delirium at discharge and classified as persistent delirium (**Figure 1**).

The average age of the study subjects was 70.7±4 years. About half of the subjects were women (51.2%), comorbidities were chronic kidney disease (52.50%), diabetes mellitus (50%), and hypertension (50%). (**Table 1**).

Table 2 shows differences in hs-CRP, pNF-H, S100B, and NLR levels at varying severity of delirium. There were significant differences in hs-CRP and NLR levels between mild, moderate, and severe delirium, with the highest value in severe delirium.

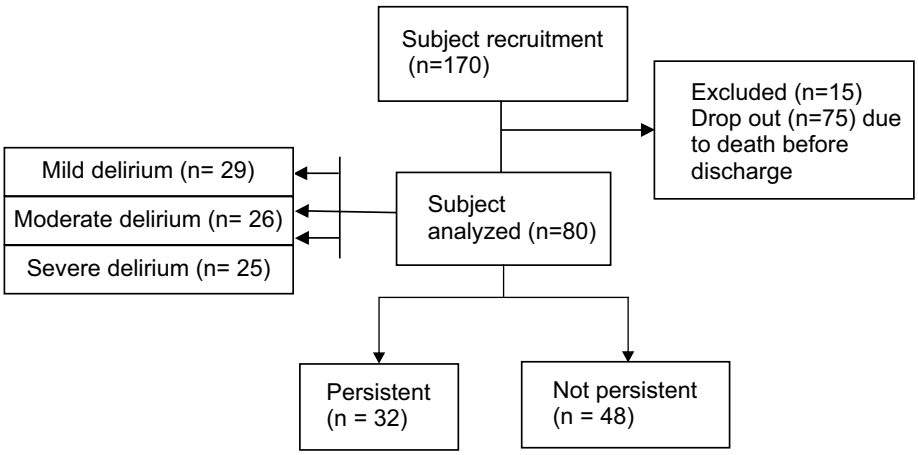

Figure 1. Subject recruitment flow.

Table 1. Subject characteristics (n=80).

Characteristics	Total	Persistent delirium (n=32)	Non-persistent delirium (n=48)
Age (mean ± SD)	70.7±7.4	71.5±7.3	70.2±7.6
Gender			
Male (n, %)	39 (48.8)	12 (37.5)	27 (56.3)
Female (n, %)	41 (51.2)	20 (62.5)	21 (43.8)
Comorbidities (n, %)			
Diabetes	40 (100.0)	18 (45.0)	22 (55.0)
Hypertension	40 (100.0)	18 (45.0)	22 (55.0)
Cardiac disease	26 (100.0)	14 (53.8)	12 (46.2)
Chronic kidney disease (CKD)	42 (100.0)	19 (45.2)	23 (54.8)
Delirium severity			
Mild	29 (100.0)	2 (6.9)	27 (93.1)
Moderate	26 (100.0)	9 (34.6)	17 (65.4)
Severe	25 (100.0)	21 (84.0)	4 (16.0)

SD, standard deviation

Table 2. Hs-CRP, pNF-H, S100B, and NLR levels at the baseline.

Variables	Total	Mild delirium (n=29)	Moderate delirium (n=26)	Severe delirium (n=25)	P value
hs-CRP (mg/L)	13.59±0.75	13.36±0.79	13.56±0.78	13.88±0.59	0.038
pNF-H (pg/mL)	598 (18.36-4759.94)	605.86 (18.36-3309.20)	542.12 (25.28-4759.94)	643.27 (82.09-4669.88)	0.813
S100B (pg/mL)	21.73 (17.49-531.16)	22.74 (17.91-36.99)	21.53 (18.13-99.23)	20.89 (17.49-37.68)	0.074
NLR	9.35 (1.00-46.50)	6.80 (1.00-31.00)	9.50 (3.60-46.00)	11.90 (2.80-46.50)	0.026

Table 3. Relationship of hs-CRP, pNF-H, S100B, and NLR levels with delirium persistence.

			Bivariate analysis		Multivariate analysis	
Variable	**Cut off**	**AUC (95% CI)**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
hs-CRP (mg/L)	13.61	0.627 (0.504-0.751)	2.54 (1.01-6.39)	0.045	2.54	0.047
pNF-H (pg/mL)	549.00	0.508 (0.370-0.640)	0.75 (0.30-1.83)	0.523		
S100B (pg/mL)	21.58	0.459 (0.326-0.592)	0.53 (0.21-1.31)	0.167	0.74	0.583
NLR	9.35	0.538 (0.409-0.668)	1.52 (0.62-3.74)	0.361		

AUC *area under the curve*, OR *odd ratio*

The analysis results showed that hs-CRP was significantly associated with persistent delirium events. Subjects with hs-CRP levels exceeding 13.61 had a 2.5-fold increased risk of delirium persistence, whereas pNF-H, S100B, and NLR levels showed no significant association with delirium persistence.

DISCUSSION

The study found high levels of hs-CRP (exceeding 13.61 mg/L) can predict the risk of persistent delirium (OR 2.54, 95%CI 1.01-6.39), but this is not the case with pNF-H, S100B, and NLR.

In systemic inflammatory conditions, neutrophils activate and cross endothelial cells in the vascular brain, and release reactive oxygen species (ROS) and proteases, which will cause the destruction of endothelial cell arrangement. Disruption of the blood-brain barrier will increase the transport of cytokines to the brain. These cytokines will activate microglia that produce inflammatory markers and reactive oxygen species (ROS).[12,13] The formation of ROS by neutrophils and microglia causes oxidative stress that leads to neuronal damage and apoptosis.[14] Endothelial dysfunction will cause impaired blood flow and the release of various biochemical mediators resulting in delirium.[15] Systemic inflammation will continue to be neuroinflammatory and cause various activation of microglia and astrocytes which will excrete S100B, a calcium-bound protein that will increase neuronal inflammatory conditions and blood-brain barriers' permeability. Damage to the blood-brain barrier will increase the transport of cytokines to the brain leading to damage to the synapse.[7]

High sensitivity-CRP is a relatively stable marker for a long time and has high sensitivity, in contrast to S100B, which has a short half-life so that within 24 hours, it returns to normal levels.[16] Evident in this study, S100B levels are generally normal (<100 pg/mL).

Ischemia and neuron apoptosis lead to neuronal damage characterized by high pNF-H levels in delirium subjects. The pNF-H levels found in neuron axon damage can last up to 21 days. Almost all delirium patients in this study had positive pNF-H levels and did not differ in those who were persistent or not. Hayakawa et al. concluded that S100B could be used as an early marker, while pNF-H is used as a delayed marker in neuronal injury.[17]

Research on the relationship between CRP and persistent delirium is still lacking. Some existing studies only link CRP levels to the occurrence of delirium. Zhang, who examined CRP levels in ICU patients, found an increase in CRP >8.1 mg/L in 24 hours associated with a 4-fold increased risk of delirium. Patients with delirium had a longer treatment duration than patients without delirium. This study did not record the incidence of persistent delirium.[18] Research on patients undergoing vascular surgery also showed CRP as a marker for an increased risk of post-surgical delirium events.[19] (Pol). Vasunilashorn's study (2017) found high CRP levels associated with delirium duration.[20] McGrane (2011) found a link between hs-CRP levels and the shorter duration of delirium free in critically ill patients.[21]

This study supports the role of hs-CRP as an inflammatory marker in predicting the risk of persistent delirium. Further research with larger sample size and different subjects is needed to support this finding. High levels of hs-CRP also indicate the severity of the inflammatory process occurring in delirium patients. The limitation of this study is the definite onset of delirium was unclear because patients had had delirium when admitted to the ward.

CONCLUSION

High sensitivity of c-reactive protein but not pNF-H, S100B, and NLR could be used to predict the risk of persistent delirium.

CONFLICT OF INTEREST

All authors declare no conflict of interest related to this study.

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Diagnostic Model of COVID-19 Infection Based on the Combination of Clinical Symptoms, Chest Radiography and Laboratory Test

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ABSTRACT

Background*: COVID-19 is an infection caused by SARS-COV 2.For screening the patient, Rapid antigen for COVID-19 is used with a high diagnostic value. However, there are still some cases of false-negative even with clinical symptoms suggesting COVID-19.Undetected COVID-19 patients certainly will increase transmission. A simple and practical diagnostic model, using determining factors, is required to guide physicians through a quicker decision making process, especially when deciding the need for the isolation rooms for patients with COVID-like symptoms.* ***Methods****: This study is a cross-sectional study. The study was conducted at CiptoMangunkusumo Hospital, Jakarta.History of contact with COVID-19, clinical symptoms, laboratory examination, and chest radiograph data were taken from medical records. Bivariate and multivariate analyses were conducted to assess the effect sizes of patient factors on the diagnostic results.ROCcurve and Hosmer-Lemeshow calibration was used to make the scoring.* ***Results****: There were 187 patients with the majority of subjects in the age group < 60 years old. The selected variables in this scoring systemwere contact history,fever/history of fever, dyspnea with respiratory rate >20 breaths/minute, leucocyte ≤ 10.000 cells/mLand typical chest radiography. The area under the curve for this model was 0,777 (CI95% (0,706-0,847), P<0,001). The probability was 82% with a cut-off point ≥ 4.* ***Conclusion****: Determinant models based on the combination of contact history, presence or history of fever, dyspnea, leucocyte count ≤ 10.000 cells/mL and typical chest radiography provides good accuracy to aid physicians in managing isolation room needs for patients with suspected COVID-19.*

Keywords**:** *COVID-19, SARS-CoV 2 diagnostic model, scoring.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a challenging health problem in the world, with rapid disease progression. Up until April 19th, 2022, there had been over 500 million global cases of COVID-19, with Indonesia being one of many countries with a high case rate. As of April 19th, 2022, Indonesia had recorded more than four million confirmed cases, with 155.937deaths.[1]

The approach of history taking, contact history, and ancillary tests are used to diagnose COVID-19. The clinical symptoms may be varied and atypical. Fever is the most common symptom. The other symptoms are respiratory symptoms (cough, dyspnea, rhinorrhea, and sore throat), systemic viral infection symptoms (malaise, myalgia, headache), and gastrointestinal symptoms (nausea, vomit, diarrhoea, abdominal pain). From some studies the ancillary tests for COVID-19 are haematology, laboratory test, and chest radiography. The haematology test in COVID-19 typically shows leucopenia, leucocytosis, lymphocytopenia, and increased neutrophil to lymphocyte ratio (NLR). In chest radiography, a lesion such as infiltrate/opacity/consolidation with bilateral peripheral distribution and a lower lobe predominance would typically be seen.[3,4]

The diagnostic gold standard for COVID-19 is *real-time polymerase chain reaction* (RT-PCR). For screening the patient, rapid antigens are usually used. However, there are cases in which the COVID-19 infection is not detected by rapid antigen testing. The longwait times required for PCR results and the lower sensitivity of rapid antigen testing leads to an increased transmission risk. If the patient is clinically suspicious for COVID-19, but screening results are negative, isolation should be carried out while waiting for the PCR results. For this reason, a clinical guide is required to determine whether a patient needs an isolation room. This study aimed to build a diagnostic model by using simple, widely available and used parameters. The final scoring system could add diagnostic value and guide physicians through a better decision making process, especially for patients with COVID-19 like syndromes.

METHODS

This study was a cross-sectional study. Secondary data was used with consecutive sampling methods. The inclusion criteria were COVID-19 suspected patients, aged ≥18 years old, and treated at Cipto Mangunkusumo Hospital, Jakarta, from March to June 2020. The exclusion criteria were patients who had incomplete laboratory tests and chest radiography, suffered from an autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis), chronic kidney disease stage V, or severe hepatic disease. Sample sizes required for this study were calculated using the rule of thumb formula. Variables analyzed in this study were contact history, fever, respiratory symptoms, systemic viral infection symptoms, gastrointestinal symptoms, typical abnormalities of chest radiography, leucocyte (≤ 10.000 *cells/μL*), lymphocyte (≤ 1.500 *cells/μL*), NLR (≥ 5,8), C-reactive protein (CRP ≥ 5 mg/L). Samples were collected and analyzed by different independent investigators to prevent any potential bias.

The definition of contact history was people with a history of physical contact or in the same room (radius <1m) with confirmed cases of COVID-19 without using standard personal protective equipment (PPE) within 2 days before onset until 14 days after onset. The definition of fever was body temperature ≥ 37.5^{0}C at the first coming in admission or history of fever within 14 days before admission. The respiratory symptoms include cough and/or dyspnea with frequency > 20 breaths/minute, and/or sore throat and/or *rhinorrhea*. Systemic viral infection symptoms include headache and/or myalgia and/or malaise. Gastrointestinal symptoms include nausea and/or vomiting, and/or diarrhoea, and/or abdominal pain. The definition of a typical abnormality of chest radiography was an abnormality in chest radiography including infiltrates or opacities or consolidation with bilateral and peripheral distribution, predominant in the lower lobes. Data was analysed using Statistical Product and Service Solution (SPSS) version 23.0 with univariate, bivariate, and multivariate analyses. Variables with $p < 0.25$ from bivariate analysis were included in the multivariate analysis. We used a logistic regression technique to determine each variable's contribution to COVID-19 diagnosis. The scoring system was made by using coefficient (B) and standard error. The scoring system has also been tested with the *receiver operating characteristics* (ROC) curve and calibrated using the *Hosmer-Lemeshow test.*

Ethics Approval and Consent to Participate

The data were taken from medical records, thus we did not need informed consent from

the participants. This study was approved by the Institutional Review board at University of Indonesia, reference number: KET-576/UK2.F1/ETIK/PPM.00.02/2020.

RESULTS

This study was conducted from March until June 2020. We included 196 patients, of which 9 patients were excluded (4 systemic lupus erythematosus patients, 2 hepatic cirrhosis patients, and 3 stadium V chronic kidney disease patients). Hence, one hundred eighty-seven patients were analyzed. The majority of patients were older than 60 years old (65.2%) and male (53,4%) as seen from **Table 1**.

Hypertension (18.7%) and diabetes mellitus (18.7%) are the most common comorbid diseases (**Table 1**). There are 70 COVID-19-confirmed cases. Confirmed cases are defined as cases with at least one positive RT-PCR result, whereas negative cases are defined as cases with at least two negative RT-PCR results as seen in **Table 1**.

Table 1. Demographical and clinical characteristics of subjects (n=187).

Variables	No. of sample (%)
Age	
< 60 years old	122 (65.2)
≥ 60 years old	65 (31)
Gender	
Male	100 (53.5)
Female	87 (46.5)
Contact History	
in positive patient	22 (12)
in negative patient	165 (88)
Swab Result	
Positive	70 (37.4)
Negative	117 (62.6)
Comorbidity	
Diabetes Mellitus	35 (18.7)
Hipertension	35 (18.7)
Malignancy	24 (12.8)
CAD	13 (7)
Tuberculosis	11 (5.9)
Chronic Kidney Disease	12 (6.4)
Stroke	7 (3.7)
Heart Failure	3 (1.6)
COPD	2 (1.1)
Asthma Bronchial	2 (1.1)
Leucocyte, cells /uL	
≤ 10.000	97 (51.9)
> 10.000	90 (48.1)
Lymphocyte, cells /uL	
< 1500	137 (73.3)
≥ 1500	50 (26.7)
NLR[a]	
< 5,8	97 (51.9)
≥ 5,8	90 (48.1)
CRP[b] **(mg/L)**	
< 5	31 (16.6)
≥ 5	156 (83.4)

[a]NLR: neutrophil to lymphocyte ratio;[b]CRP: C-reactive protein

All of the included subject had at least one symptoms. Fever and history of fever are reported in 65.2% patients. The most common respiratory symptom is cough (72.2%) and the most common gastrointestinal symptom was nausea (23.5%) as seen in **Table 1**.

Leucocyte ≤ 10,000 cells/uL is found in 51.9% of cases, Lymphocyte ≤ 1500 cells/μL in 73.3% of cases, NLR ≥ 5.8 in 51.9% of cases and CRP ≥ 5 mg/L in 83.4% of cases. Typical abnormality of chest radiograph is shown in 20.9% of patients as seen in **Table 1**. The variables from bivariate analysis with $p < 0.25$ were then included in the multivariate analysis. After multivariate analysis,some of the variables with $p > 0.05$ were excluded from scoring.

Results from the multivariate analyses show that the contact history, presence of dyspnea, leucocyte count ≤ 10,000 cells/uL, typical chest radiography are statistically significant predictors, as seen on **Table 2-3**. Although fever history is not statistically significant in the multivariate analysis, it is a clinically important factor that should not be disregarded when interpreting the results of the scoring system.

In the multivariate analysis, we created a score for each variable. Contact history with a confirmed COVID-19 patients is worth 3 points, fever/history of fever, 1 point, dyspnea with respiratory rate 20 breaths/minute, 2 points, leucocyte ≤ 10,000 cells/uL 2 points and typical chest radiography 2 points. The total score is 10 points as seen from **Table 4**.

From the ROC curve analysis, the area under the curve is 0.77 with a cut-off point of 4 (**Figure 1A**). This diagnostic value for a scoring system with a cut-off point of 4 has good specificity (88.03%) as seen from **Figure 1**.

DISCUSSION

The cumulation of clinical symptoms and workup results can be utilized to predict the diagnosis of COVID-19. Scoring systems provide a simple assessment tool that can supplement

Table 2. Analysis of clinical symptoms for the diagnosis of COVID-19.

Variables	COVID-19 N (%)	Non-COVID-19 N (%)	P Bivariate	PMultivariate	OR (CI 95%)
Contact History					
Yes	18 (81,8)	4 (18.2)	**<0.001**	**<0.001**	8.673 (2.573-29.231)
No	52 (31.5)	113 (68.5)			
Fever/History Fever					
Yes	49 (40,2)	73 (59.8)	0.185	0.192	1.658 (0.776-3.539)
No	21 (32.3)	44 (67.7)			
Cough					
Yes	53 (39.2)	82 (60.8)	0.255		
No	17 (24.3)	35 (29.9)			
Dyspnea					
Yes	16 (47.0)	18 (53.0)	**0.139**	0.024	2.708 (1.141-6.503)
No	54 (35.5)	99 (64.5)			
Sore Throat					
Yes	16 (45.7)	19 (54.3)	**0.176**	0.671	0.820 (0.328-2.048)
No	54 (35.5)	98 (64.5)			
Rhinorrhea					
Yes	6 (30.0)	14 (70.0)	0.320		
No	64 (38.3)	103 (61.7)			
Nausea					
Yes	14 (31.8)	30 (68.2)	**0.243**	0.387	0.679 (0.283-1.631)
No	56 (39.1)	87 (60.9)			
Vomiting					
Yes	12 (63.1)	19 (36.9)	0.512		
No	58 (37.1)	98 (62.9)			
Diarrhoea					2.742
Yes	11 (55.0)	9 (45.0)	**0.072**	0.085	(0.871-8.632)
No	59 (35.3)	108 (64.5)			
Abdominal Pain	7 (31.8)	15 (68.2)	**0.371**		
Yes	63 (38.1)	102 (61.9)			
No					
Myalgia					
Yes	3 (20.0)	12 (80.0)	**0.118**	0.093	0.242 (0.046-1.268)
No	67 (38.9)	105 (61.1)			
Headache					
Yes	7 (31.8)	15 (68.2)	**0.371**		
No	63 (38.1)	102 (61.9)			
Malaise					
Yes	24 (36.3)	42 (63.4)	**0.476**		
No	46 (38.0)	75 (62.0)			

Table 3. Analysis of ancillary tests for diagnosis of COVID-19.

Variables	COVID-19 N (%)	NON COVID-19 N (%)	P Bivariate	P Multivariate	OR (CI 95%)
Chest Radiography					
Typical	21 (53.8)	18 (46.2)	0.015	0.003	3.487 (1.515-8.026)
Atypical	49 (33.1)	99 (66.9)			
Leucocyte (≤ 10.000)					
Yes	50 (51.5)	47 (48.5)	< 0.001	0.024	2.381 (1.120-5.063)
No	20 (22.2)	70 (77.8)			
Lymphocyte(≤1.500)					
Yes	49 (35.7)	88 (64.3)	0.270		
No	21 (42)	29 (58)			
NLR(≥5,8)					
Yes	24 (24.7)	73 (75.3)	<0.001	0.071	0.504 (0.234-1.061)
No	46 (51.1)	44 (48.9)			
CRP(≥5)					
Yes	54 (34.6)	102 (65.4)	**0.058**	0.656	0.803 (0.307-2.104)
No	16 (51.6)	15 (48.4)			

Table 4. C-COVID score (clinical COVID score).

Variables	Assesment	Score
Contact History with COVID-19	Yes	3
Fever ≥ 37,5 / Fever History	Yes	1
Dyspnea (RR > 20breaths/minute)	Yes	2
Leucocyte (≤ 10.000 /uL)	Yes	2
Typical Chest Radiography (Infiltrat/Opacity/Consolidation with bilateral, peripheral, and lower zone predominant)	Yes	2
Total		10
Score ≥ 4 (at least 1 clinical symptoms included) Suspect COVID 19: (Probability 82%), PPV 74% NPV 77%		

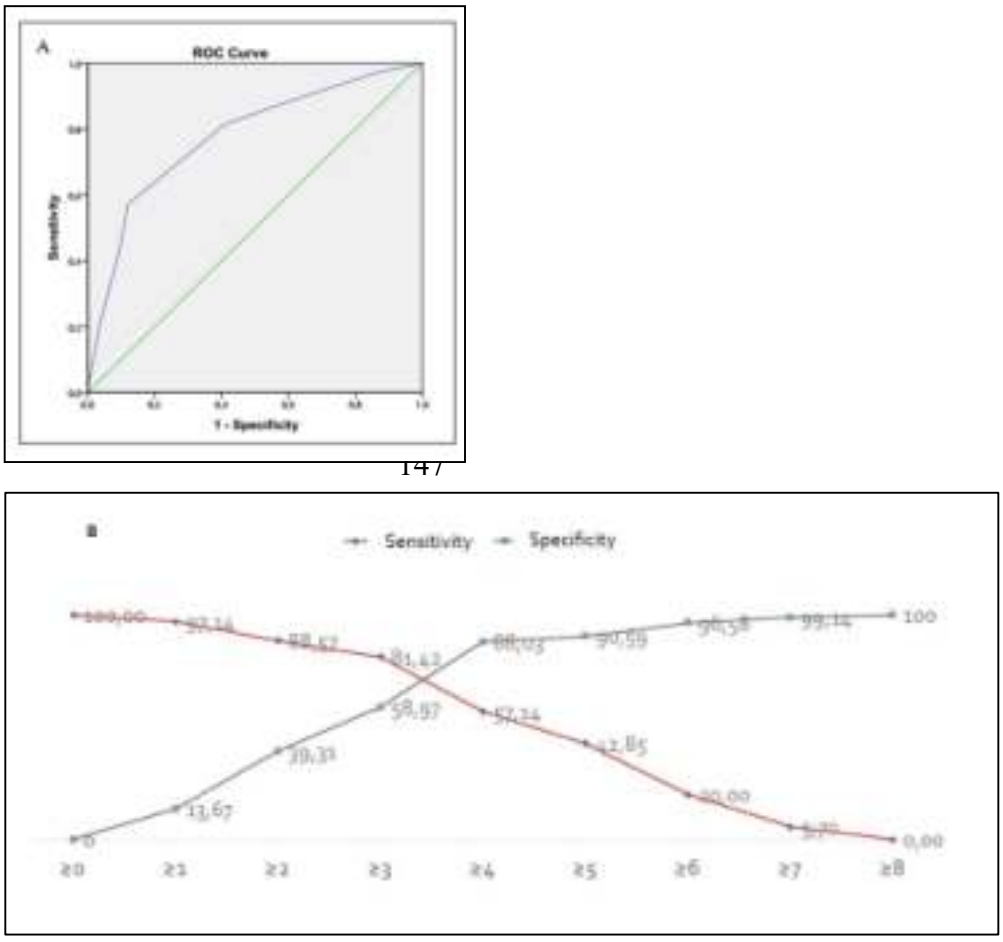

Figure 1. A. ROC curve of the scoring system. B. Cut-off curve between senstivity and specificity of the scoring system.

clinician judgment. This study was aimed to create a diagnostic scoring system for COVID-19 based on common clinical symptoms, simple laboratory tests and diagnostic imaging which are available in most primary healthcare centers. Our scoring system consisted of 5 variables: contact history with COVID-19 patients, presence or history of fever, dyspnea with respiratory rate > 20 breaths/minute, leucocyte count ≤ 10.000 cells/uL and typical chest radiography.

In this study, the information can be easily obtained from history taking. Contact history was one important determining factor in this study. Multivariate analysis showed that contact history

was statistically significant with OR 8.673 (CI 95% 2.573-29.231, p < 0.001). Droplets from coughing, sneezing, or talking may occur within < 1 meter distance. This theory is reinforced by a study from Chu et al., who showed that physical distancing over 1 meter has a better protective effect than < 1 m (OR 0.18).[8] SARS-CoV-2 will stay in fomites (contaminated object or environment): for 2 hours in plastic and stainless steel, 4 hours in copper, and 24 hours in carton.[9] A study by Van Doramalen et al. reported that SARS-CoV-2 would live in aerosol nebulizer at least for 3 hours; and to 16 hours long in another study. Therefore, airborne transmission may occur. The growing evidence that supports droplets as well as airborne particles as the transmission mechanism of SARS-CoV-2 emphasises that contact history in suspected patients is imperative.

Dyspnea are not as frequent as fever or cough. This may happen because dyspnea appears after 3 days of onset. Although the frequency of dyspnea is not very frequent, but dyspnea is the most common symptom which bring patients to the hospital. Dyspnea was statistically significant in this study with OR 2.708 (CI 95% (1.141-6.503), p= 0.024). Song et all also reported that dyspnea was significant for diagnosis with COVID-19.[5] In this study, we combine subjective symptoms of dyspnea and objective assessment of tachypnea (>20 breaths/minutes), so it will be more specific for helping diagnosis COVID-19.

Fever is the most common symptom in COVID-19. But in this study, fever was not statistically significant. It is hypothesized that there was potential bias in collected data. Because we conducted the data from medical record, which is we did not know whether the temperature at that time was influenced by the previous use of antipyretic drug or not. The result of this study contradict with a meta-analysis by Cao et al. reported that fever occurred in 87.3% of patients. The meta-analysis study from Islam MA (2021) showed that the prevalence of fever in COVID-19 patient was high (79.43%), especially in severe and critical illness patient (91.69%). Therefore, fever is an important clinical presentation of COVID-19. We decided to include this symptom in our scoring to reduce the risk of missed diagnosis.

Several studies have emphasized evaluation of abnormal leucocyte in COVID-19 patients, with both leucopenia and leucocytosis. Leucocyte£ 10.000 cells/ml was one of the variables which was statistically significant with OR 2.381 (CI 95% (1.120-5.063), p=0.024). Leucocyte have well-known role in immunity response to infection. Change in leucocyte indicate a systemic inflammatory condition caused by the patient's immune system. Normal leucocyte or lower (leucopenia) usually happens in the initial stage of infection. Sun et al. reported that confirmed COVID-19 patients had lower leucocyte than non-COVID-19 patients (p < 0.001).[12-14] But during observation with severe condition have higher leukocyte level (leukocytosis) than those with mild-moderate condition. Therefore, leukocyte count may assist in assessing the probability of patient having more severe disease. Additionally, differential count components in COVID-19 patients show lower eosinophil and lymphocyte levels and higher levels of neutrophils and monocytes compared to healthy people.[15] Peng et al. found that NLR showed significant positive correlations with PSI, CURB-65 and MuLBSTA. Increased neutrophil-to-lymphocyte ratios (NLR) may serve as a predictor for severity of disease. It explained, that our patient had mild moderate symptoms, which was the reason the increased NLR was not significant in this study.[5]Besides that,lymphopenia (absolute lymphocytecount(ALC) < 1500 cells/mL) was not statistically significant. This finding agreed with Mardani et al. and Song et al. also reported no significant relation between lymphocyte and diagnosis COVID-19. In the initial stage of SARS-CoV-2 infection, the lymphocyte may be normal. As severity increases, the lymphocyte would decrease, so it actually makes lymphocytes an excellent indicator of the severity of COVID-19, but not for diagnosis COVID-19. A systematic review by Huang et al. reported that COVID-19 patients had three times the risk for adverse outcomes if they had had leucocytes < 1.100 cells /mL.[16]

CRP ≥ 5 mg/dL was statistically significant in this study. This result is similar to Ferrari et al. Some studies have indeed reported increased

CRP in COVID-19 patients. However, this protein is not an adequate diagnostic marker because of its low specificity for COVID-19. A study by Wang et al. showed an increase in CRP following a lung lesion in COVID-19. Therefore, CRP is more effective as an indicator for prognosis rather than for diagnosis of COVID-19.[17,18]

Typical abnormalities in chest radiography occurred in 20.9% of the subjects. As many as 53.8% from those groups were confirmed cases of COVID-19. The results from multivariate analysis showed a statistically significant association with OR 3.487 (CI95% (1.515-8.026), p= 0,003), as supported by Wong et al. who described a typical abnormality of COVID-19 as multifocal consolidation or opacity with bilateral distribution in the peripheral and lower lobe of the lungs.[4,19] Cozy et al. described opacities or reticular nodular consolidation with bilateral peripheral distribution and lower zone predominance as a typical radiograph lesions in COVID-19. This lesion is caused by activation of ACE-2 receptors, which are expressed more in pneumocytes located distally. This provides evidence that SARS-CoV2 tends to infect the distal areas.[20,11]Study from Smith DL et al. showed that the typical chest X ray of COVID-19 (patchy or confluent, GGO or consolidation in the peripheral area and mid to lower lung zone distribution) had high specificity (96.6%) so that the typical chest x ray is good for guiding the diagnosis.[21]

Scoring systems are proposed as diagnostic tools to help clinicians manage suspected patients. It includes history of contact, clinical symptoms and simple laboratory tests and imaging. This scoring system is simple, cost-effective and accessible workup, include: contact history with COVID-19 patients (3 points), fever/history of fever (1 point), dyspnea with respiratory rate > 20 breaths/ minute (2 points), leucocyte ≤ 10,000 cells/uL (2 points) and typical chest radiography (2 points). The total score is 10 points. ROC analysis revealed AUC = 0.77 for score cut-off ≥ 4 suggested that patients of suspected COVID-19. Hence, we recommend using a cut-off point ≥ 4 for the score and as importantly, taking into account the clinical symptoms. This scoring system has been tested and will be able to establish a suspected COVID-19 diagnosis with a specificity of 88.03%. Calibration tests for this scoring system, using the Hosmer and Lemeshow Test, resulted in a p-value of 0.590, indicating good validation.

This scoring may be used for clinical practice. Patients with a score ≥ 4 can be recommended to be treated in isolation while waiting for the PCR results. By using this scoring, the physician can decide the needs for isolation room for patient and will reduce the risk of transmitting COVID-19 infection. In addition, patients with negative antigens, but with a 4 score or more than 4, must also remain vigilant considering that antigen is not the gold standard so that COVID-19 cannot be excluded.

On the other hand, this study has potential biases and limitations in the form of sample size and limited sample collection time. The sample size was quite small because the data in this study was only collected from one center (Cipto Mangunkusumo Hospital), as one of the COVID-19 referral centers in Jakarta. Therefore, wider range of populations from multiple center is still needed. Careful interpretation and implementation in other centers, involving patients with more variable demographical characteristics, is warranted to evaluate the reliability and validity of this scoring system, in the assessment of suspected COVID-19 cases. This study is a one-center study, which adds to its limitations. In addition, the study used secondary data and was conducted at the beginning of the COVID-19 pandemic in Indonesia, and so the study conditions may differ from current conditions.

Further research can be carried out in multiple centers and with a larger sample size, to ensure that the results of previous studies can be externally validated in different populations.

CONCLUSION

This diagnostic model, taking into consideration contact history, fever/history of fever, dyspnea with respiratory rate > 20 breaths/ minute, leucocyte ≤ 10,000 cells/μL and typical chest radiography, provides diagnostic value with a good specificity to help direct decision making in patients with suspected COVID-19.

Patients with a score ≥ 4 can be recommended to be treated in isolation while waiting for the PCR results.

ABBREVIATION

COVID-19:Coronavirus Disease 2019; SARS-CoV-2:Severe Acute Respiratory Syndrome-Coronavirus-2; WHO:World Health Organization; NLR: Neutrophil to lymphocyte ratio; RT-PCR:Reverse transcription polymerase chain reaction; PPE : Personal protective equipment; ROC:Receiver operating characteristics; SPSS: Statistical Product and Service Solution; OR:Odds ratio; CI:Confidence interval; CRP:C-reactive protein; PPV : Positive predictive value; NPV:Negative predictive value; LR:Likelihood ratio; ACE-2 : Angiotensin converting enzyme-2; ALC:Absolute lymphocyte count.

CONFLICT OF INTEREST

The authors declare no competing interests.

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Learning Intelligent for Effective Sonography (LIFES) Model for Rapid Diagnosis of Heart Failure in Echocardiography

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ABSTRACT

Background: *The accuracy of an artificial intelligence model based on echocardiography video data in the diagnosis of heart failure (HF) called LIFES (Learning Intelligent for Effective Sonography) was investigated.* ***Methods:*** *A cross-sectional diagnostic test was conducted using consecutive sampling of HF and normal patients' echocardiography data. The gold-standard comparison was HF diagnosis established by expert cardiologists based on clinical data and echocardiography. After pre-processing, the AI model is built based on Long-Short Term Memory (LSTM) using independent variable estimation and video classification techniques. The model will classify the echocardiography video data into normal and heart failure category. Statistical analysis was carried out to calculate the value of accuracy, area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR).* ***Results:*** *A total of 138 patients with HF admitted to Harapan Kita National Heart Center from January 2020 to October 2021 were selected as research subjects. The first scenario yielded decent diagnostic performance for distinguishing between heart failure and normal patients. In this model, the overall diagnostic accuracy of A2C, A4C, PLAX-view were 92,96%, 90,62% and 88,28%, respectively. The automated ML-derived approach had the best overall performance using the 2AC view, with a misclassification rate of only 7,04%.* ***Conclusion:*** *The LIFES model was feasible, accurate, and quick in distinguishing between heart failure and normal patients through series of echocardiography images.*

Keywords: *Artificial intelligence, machine learning, echocardiography, heart failure.*

INTRODUCTION

Cardiovascular disease remains the leading cause of death globally.[1] Current guidelines for diagnosing heart failure can only detect symptomatic and end-stage heart failure patients, who comprise only 12.2% of the population. However, heart failure patients who are asymptomatic or have a high risk of developing heart failure occupy 56% of the population and generally go undetected; hence affecting the prognosis of these patients.[2]

On the other hand, numerous studies have shown that artificial intelligence (AI) models have decent diagnostic quality in assisting the work of cardiologists, including diagnosing heart failure based on ECG and echocardiographic data.[3-5] AI has proven to help with an accurate diagnosis, clinical management, and patient care.[6] AI in cardiovascular imaging can also reduce costs, avoid missed diagnoses, false-positive diagnoses, inter-observer variability, and improve time efficiency.[7] However, no studies have yet built AI algorithms to diagnose heart failure patients based on echocardiography videos. Specifically, no studies have optimized the use of many echocardiography views (e.g., long axis, 4-chamber view, and 2-chamber view) nor provided automatic measurement of EF and E/A ratio.

Thus, this study proposes an artificial intelligence model called LIFES (Learning Intelligent for Effective Sonography) developed in this study. It is the first study of artificial intelligence in the field of echocardiography in Indonesia that can quickly, precisely, and cost-efficiently distinguish regular patients from heart failure patients in the Indonesian population. The study results are expected to be used in heart centers throughout rural areas in Indonesia, especially in peripheral regions, so that timely and accurate heart failure diagnosis becomes no more challenging.

METHODS

The research design is a cross-sectional diagnostic test using consecutive sampling. The target population in this study is echocardiography videos of clinically diagnosed chronic heart failure and normal patients from the accredited echocardiography lab in Harapan Kita National Heart Center. This study was approved by the Harapan Kita National Heart Center Institutional Review Board. Echocardiographic examinations were carried out by a cardiologist or trained cardiovascular technicians using Vivid E9 echocardiography machines and M5Sc transducers. These data were analyzed in the workstation (EchoPAC PC; GE Vingmed Ultrasound US). Echocardiograms were obtained using apical 4-chamber (A4C), apical 2-chamber (A2C), and parasternal long-axis (PLAX). In assessing left ventricular structure and function, multiple features were extracted, including velocity, left ventricular end-systolic and end-diastolic volume and ejection fraction as calculated by Simpson's method[8], the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'), left atrial volume likewise left atrial volume index (LAVI) using biplane length method. The data was then saved in the cine-loop format for up to 5 heartbeat cycles with both left ventricles and left atrium clearly and wholly visualized. The frame rate of each image is 50 to 90 frames/second. Then, the results were validated by an expert echocardiologist based on national guidelines to reduce inter-observer variability.

Dataset Selection

The medical records for all inpatients and outpatients with chronic heart failure from January 2020 to October 2021 are obtained. Cardiologists established heart failure diagnoses based on clinical data, laboratory results, and echocardiography, which is the gold-standard method. Then, the authors screened data quality, completeness, and compatibility using our inclusion criteria. The inclusion criteria were echocardiographic data of patients with clinical presentation of shortness of breath and diagnosed as chronic heart failure by cardiologists. The echocardiography exam might be done during the patient's first encounter in clinic (non-emergency setting) or after multiple episodes of care/control. Exclusion criteria were: (1) arrhythmia, such as atrial fibrillation, (2) coexisting severe valvular heart disease, (3) incomplete echocardiography examination. The normal subjects included were completely health

population with no comorbidities, i.e., asthma or chronic obstructive pulmonary disease, with normal cardiac evaluation results. The minimum sample size is determined through the sample formula approach for diagnostic tests, where we find the minimum sample size to be 129 subjects, including a 10% possibility of dropouts.

Statistical Analysis

Statistical analysis was performed using RStudio program (version 2022.02.3+492. pro3, PBC, Boston). Numerical data are expressed as a mean or median with a standard deviation, while categorical data is presented in a percentage. Missing variables are assumed to be 'missing at random (MAR) and handled using multiple imputations. The technique has yielded unbiased results for MAR even when there is a considerable proportion of missing data.10 Next, calibration, and discrimination are carried out. Calibration is an agreement between the reported and expected outputs, which in this study are HF/normal and HFrEF/HFpEF. The calibration was analyzed using the Hosmer-Lemeshow goodness-of-fit statistical test with $p>0.05$, indicating that the score had a good calibration. Meanwhile, discrimination suggests the ability of ML to differentiate between HF and non-HF patients and is assessed using the ROC curve to obtain the AUC between the independent variable parameters and the dependent variable, then calculated the value of sensitivity, specificity, PPV, NPV, and LR.

Machine Learning Method

Our proposed method consists of two processes: pre-processing, where we prepare our data, and model training, where we train and evaluate our classification model. The overall flow of our proposed method is illustrated in **Figure 1**.

Pre-processing

We conducted several video pre-processing techniques to get the data ready for deep learning models. First, we perform cropping to get only the video's center and eliminate the unnecessary pixel from each frame. Then, we resized each frame to be 128 × 128 in width and height, respectively. Then, we perform frame down-sampling to reduce the number of frames for each video. The number of frames to use is decided according to which video has the least frame. This has to be done since the input for the deep learning algorithm is fixed in dimension. Therefore, we resized each frame to a specific size and down-sampled the number of frames for each video to a particular number of frames. Lastly, each frame is normalized by dividing each pixel by 255, resulting in a value ranging from 0 to 1.

Model Training

We split the data into train and test using StratifiedKFold cross-validation with a K value of 5. VGG16 is used to help represent video into a sequence of vectors and then train a predominant deep learning algorithm for sequential problems,

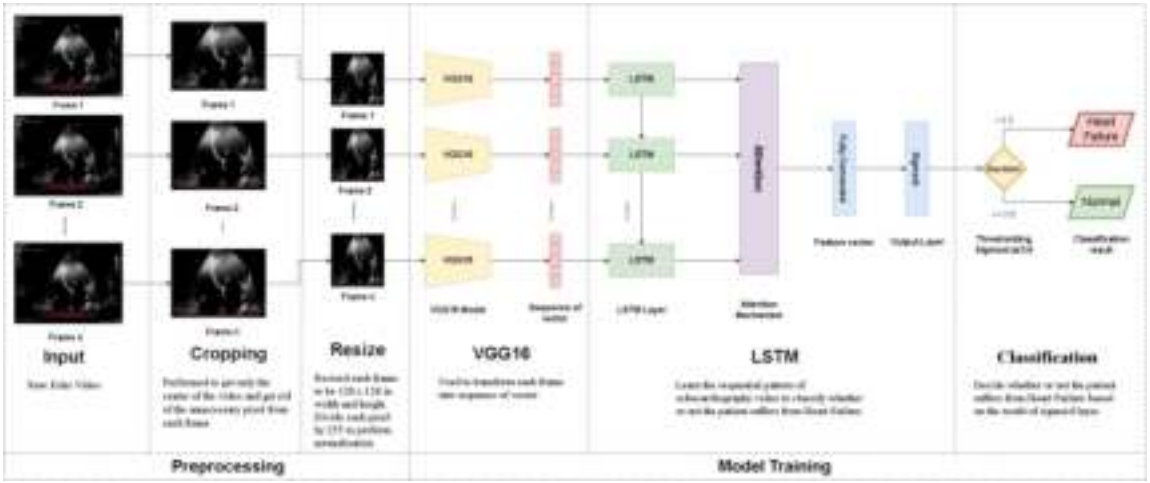

Figure 1. Illustration of the machine learning flow.

namely Long-Short Term Memory (LSTM).

VGG16 is a convolutional neural network (CNN) model developed by the Visual Geometry Group (VGG), University of Oxford13. VGG16 was trained on the Imagenet dataset and achieved state-of-the-art results in a well-known computer vision competition, Visual Recognition Challenge (ILSVRC), with an accuracy of 92,70%. VGG16 consists of 16 layers, as illustrated in **Figure 2**. Note that we only use VGG16 as an encoder to extract feature vectors out of each frame on which these feature vectors are then fed into LSTM to learn its sequential pattern; therefore, the weights and biases of VGG16 are frozen, and the softmax layer is removed.

Hochreiter first introduced LSTM to cover the limitation of recurrent neural network (RNN) that suffers from vanishing gradient problems where the gradient cannot reach every layer. This problem occurs when the model is forced to learn a very long sequence. LSTM addressed this problem by introducing the so-called "Long Term Memory" (also known as cell state) denoted as C in **Figure 3**. This cell state does not go through any non-linear activation function; hence during the gradient descent, it is this cell state derivative that can prevent the LSTM gradients from vanishing. It has been shown that LSTM can learn long data sequences better than RNN.11 A single cell of LSTM consists of several parts that are often called gates.

The first gate is called forget gate as highlighted in **Figure 4**. The forget gate is responsible to decide whether or not the model

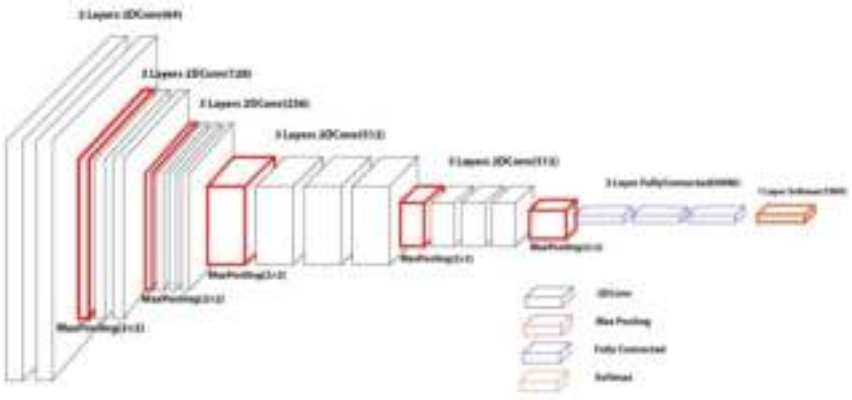

Figure 2. VGG16 architecture.

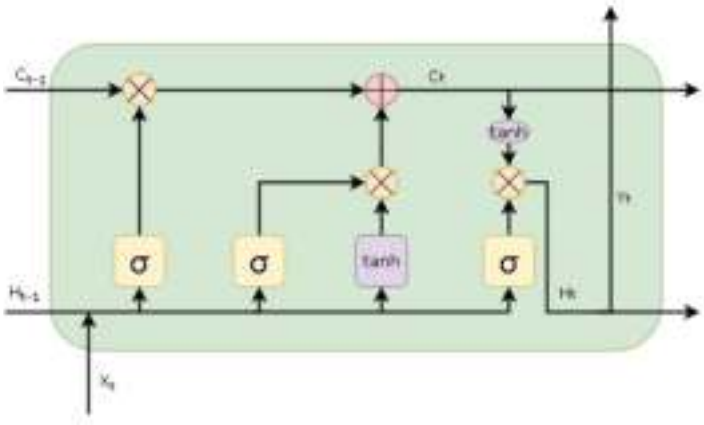

Figure 3. LSTM cell.

should keep the information from the previous timestamp. This gate uses a sigmoid activation function which produces output that's ranging from 0 to 1, this can be interpreted as how much the information from the previous timestamp is necessary for the model to remember.

The second gate is called the input gate as highlighted in **Figure 5**. The input gate is responsible to quantify the importance of the information from the current timestamp which the model will add this information to it's cell state. The input gate consists of two neurons, the first neuron (yellow rectangle) uses sigmoid activation function while the other (purple rectangle) uses tanh activation function. First, the new information along with the previous hidden state is being fed to the sigmoid neuron resulting in a value ranging from 0 to 1. Then, the same thing is fed to the tanh neuron resulting in a value ranging from -1 to 1. On top of that, both the result of the sigmoid neuron and the tanh neuron are multiplied to decide how much information and whether to add or to subtract the new information to the cell state.

The last gate is called output gate as highlighted in **Figure 6**. The output gate is the final gate of the cell, it is responsible to calculate the new hidden state based on the new information, the previous hidden state, and the new cell state. Both this new hidden state and the new cell state are fed to the next timestamp if exist. The output of this output gate will be the final output of LSTM cell on the last timestamp denoted by Yt in **Figure 6**.

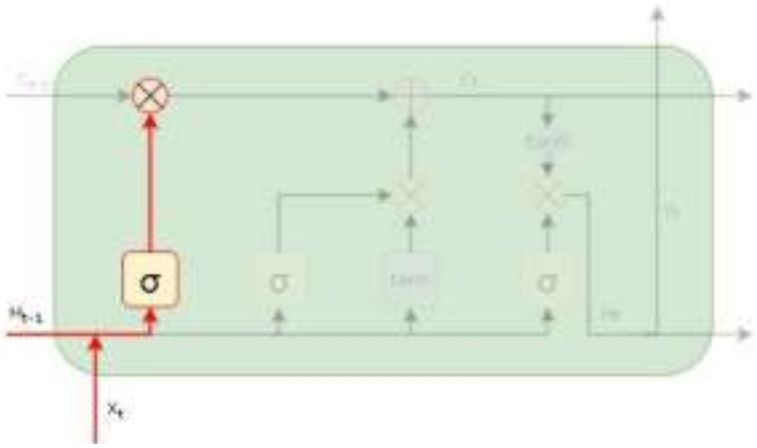

Figure 4. Forget gate.

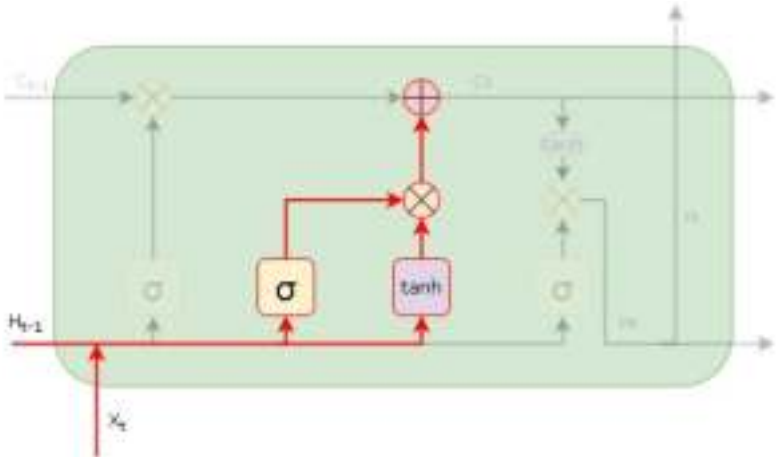

Figure 5. Input gate.

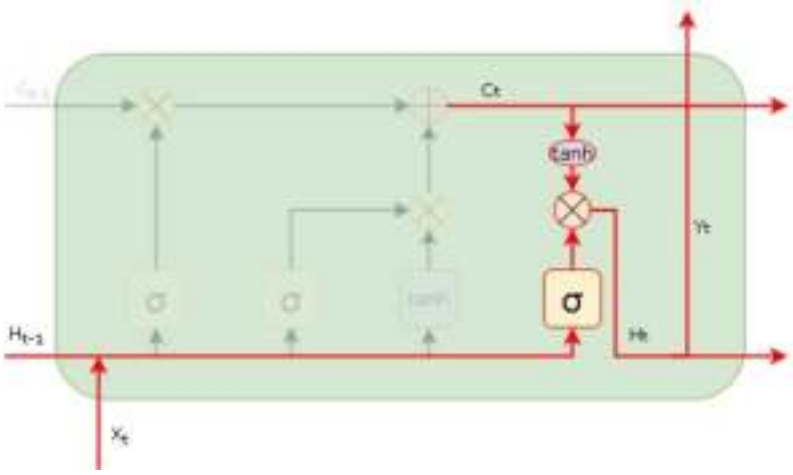

Figure 6. Output gate.

LSTM is exceptionally successful in many tasks such as handwriting recognition, speech recognition, machine translation, time-series classification, image captioning, video processing, etc.[12] We decided to use LSTM as we aim to capture the sequential pattern of a heart wall contraction in an echocardiography video with the hope that LSTM can make a reasonable prediction out of this pattern.

In addition, an attention layer is stacked on top of LSTM. When we provide a very long sequence of information, the models might ignore a few critical parts of the sequence, especially the starting part after processing the data. The attention mechanism helps the model memorize long sequences of information by taking the resulting calculation of LSTM at every timestamp. This mechanism also allows the model to pay more attention to which part of the sequence highly defines a specific class and weighs them more than others.

Lastly, the output layer consists of a sigmoid neuron. This layer is used to decide whether the patient suffers from heart failure by thresholding the output of the sigmoid neuron at 0.5, if the result of the sigmoid is greater than 0.5, then the patient is predicted to suffer from heart failure. Otherwise, the patient is predicted to be normal.

RESULTS

The characteristics of the subjects included in this study are given in **Table 1**. Male represents 81,3% and 62.5% of normal and HF patients subjects, respectively. The median age is 36 in normal subjects, compared to 58 in HF patients, and both subject groups' median/mean of SBP and DBP are within the normal range. NTproBNP values were not obtained for normal patients as it was deemed unnecessary. The EF, E Peak Vel, A Peak Vel, E'med T0, and E'lat T0 in the HF group is lower compared to the normal group. On the other hand, the E/med e', E/lat e', E/ave e', LVEDV, LVESV, LA Volume and LAVI are higher than the normal category. The wall motion abnormality was also assessed during the echocardiographic examination. It turns out that 45 show global normokinetic, 21 with regional wall motion abnormality, 14 have apical akinetic, and 19 exhibit global hypokinetic.

We conducted a binary classification experiment to distinguish heart failure. The HFpEF and HFrEF classes are merged into one category, Heart Failure, while the normal category is left unchanged. In the end, it results in two types: Normal and Heart failure. The result of this experiment is shown in **Table 2**.

The sensitivity, and specificity of A2C for discriminating between HF and normal patients were 96.29% and 87.23%, respectively. Likewise, the highest accuracy was yielded by 92.96% in A2C and had the highest F1 score of 94.54%. The sensitivity and specificity of A4C were 96.34% and 80.43%, respectively, which yielded the highest sensitivity. Meanwhile, the

Table 1. Baseline study population characteristics.

Variables	Normal (N = 48)	Heart failure (N = 90)
Physical information		
Age, years	36 ± 9.65*	58 ± 12.78*
Gender, male	39/48 (81.3%)	55/88 (62.5%)
Systolic blood pressure, mmHg	125 ± 19.33*	120.3 ± 21.51***
Diastolic blood pressure, mmHg	75 ± 11.89*	70 ± 12.08*
Height, cm	166.6 ± 8.87***	160 ± 12.59*
Weight, kg	70.11 ± 15.59***	67 ± 15.52*
NTProBNP	N/A	1806 ± 15649.4*
Echocardiographic information		
EF (55-70)	68.40 ± 6.09***	47 ± 17.09*
E/A Ratio (0,75-1,5)	1.57 ± 0.37***	1.07 ± 1.01*
E Peak Vel (70-120)	85.36 ± 18.05***	79 ± 26.47*
A Peak Vel (42-70)	55.1 ± 17.98*	67.9 ± 31.64*
E'med T0 (>8)	10.65 ± 2.43***	4.9 ± 1.76*
E'lat T0 (>10)	13.30 ± 2.18*	7.18 ± 2.57*
E/med e' (<8)	7.9 ± 2.26*	16.11 ± 8.06*
E/lat e'(<8)	6.15 ± 1.59*	10.4 ± 5.31*
E/ave e' (<8)	7.00 ± 1.36*	13.3 ± 6.10*
LVEDV 64-85	101.0 ± 20.76*	132.0 ± 73.72*
LVESV 24-37	44.0 ± 9.78*	77.4 ± 67.41*
LA Volume (A4C) <28	38.00 ± 11.22*	60.9 ± 36.16*
LAVI A4C <28	21.10 ± 6.96*	36.8 ± 24.39*

*Median ± SD; **Proportion; ***Mean ± SD

Table 2. Test performance characteristics of the model.

View	Accuracy	F1	Precision	Sensitivity	Specificity	NPV	LR+	LR-
2 Chamber	92.96	94.54	92.85	96.29	87.23	93.18	7.54	0,0425
4 Chamber	90.62	92.94	89.77	96.34	80.43	92.50	4.92	0.0455
Plax	88.28	91.01	87.35	95.00	77.08	90.24	4.15	0.0649

PLAX-view gave sensitivity and specificity of 95% and 77.08%, respectively. The overall diagnostic accuracy of A2C, A4C, PLAX-view were 92.96%, 90.62% and 88.28%, respectively.

The models yielded good diagnostic performance for discriminating between HF and normal patients. The models had the best overall performance using the 2AC view, with a misclassification rate of 7.04%.

Figure 7 shows the receiver operating characteristic (ROC) curve of the resulting models where the more the line curved to the upper left, the better the model performance. The ROC curve could be quantified by calculating the area under the curve (AUC), which we provided in the legend of the ROC figure. The random classifier indicated by the dashed red line assigns a score sampled from the uniform distribution between 0 and 1 to each instance. The rule of thumb is that no machine learning which roc curve should be under this red line. Our AUC values ranged from 0.84 (PLAX) to 0.93 (A2C). Furthermore, we performed significance testing between the test performance scores with a p-value threshold of 0.05, which we provided in **Table 3**. It can be inferred that there is no significant difference in terms of accuracy between each view compared to others.

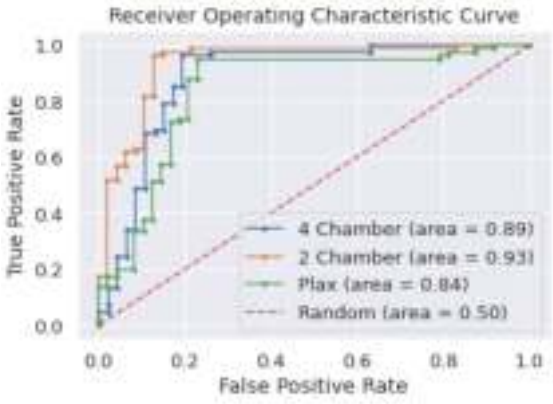

Figure 7. Receiver operating characteristic curve.

DISCUSSION

Cardiac emergencies necessitate a quick patient assessment, in addition to basic vital signs such as blood pressure, heart rate, and oxygen saturations, clinicians may need more information than vital signs. With echocardiography-ML, promptly collecting the echocardiographic helps reduce treatment options and discover plausible explanations for unstable vital signs in critically ill patients, especially in distant areas.

We provide a state-of-the-art comparison of machine-learning algorithms with human readers for diagnosing heart failure. On our findings, the mean age of the heart failure population was 58 ±12.78 and male 62.5% (**Table 1**), which was also shown previously by Reyes and colleagues with a mean age of 57.8 and predominantly male (66%) in Indonesia.[14]

The model was tested using 128 echocardiograms and showed specificity levels ranging between 77% and 87%. The highest sensitivity levels above 96% were depicted in the A4C view. We found that our approach delivered accurate information with the area under the curve (AUC) above 0.84 using the echocardiography parameter. Similarly, a single-center study by Omar AM et al. (2017) involved 130 patients and showed a slight difference of AUC of 0.853 for estimating left ventricular diastolic dysfunction.[15,17]

From our findings, the A4C view has the highest level of sensitivity compared to the other two views. A two-center study showed different results, which yielded accuracies of 97%, 97%, and 91% by using A2C, PLAX, and A4C views,

Table 3. The difference results in terms of accuracy between chamber and plax.

T-test	P-Value
2 Chamber / 4 Chamber	0.2381
2 Chamber / Plax	0.1356
4 Chamber / Plax	0.4334

respectively.[8] The A4C view is one of the hardest to achieve accuracy. Apical views (A4C and A2C) also seem to suffer the most from lower resolution images. In A4C views, the program also captures the movement of the right ventricle, which can bias learning and make it difficult to detect the endocardial border, in contrast to 2CH and PLAX views which are more focused on one side.

The high sensitivity score of 4AC is mainly caused by the imbalanced class on which we train the model. Since we merged the HFpEF and HFrEF classes into a single category, namely HF, the class distribution turned out to be 1:2 for normal and HF. As a result, the model will make prediction attempts on the majority class more often than the minority class as the misclassification is mainly caused by the model mistaking normal for HF.

There are false positives and false negatives in our results. For this reason, we have carried out internal validation with several experts to match the misclassifications we found with clinical parameters. In our analysis, there are some discrepancies, such as an increase in the left atrial pressure with the normal ejection fraction, considered heart failure but detected by the machine as normal.

Interoperator variability during echocardiography and retrieval of several echocardiographic windows with an intermittent or absent endocardial border during analysis, such as lateral or anterior windows that disappear in the systole or diastole phase, could result in misclassification. Furthermore, the shifting of several windows between A2C and A4C can also influence the false positive and false negative rates in our study, where a subset of diagnosis has normal echocardiographic features but was read as heart failure and vice versa. Hence, this supports our hypothesis that using only one view

to differentiate between HF / normal through ML is possible.

According to Khamis, H. et al. (2017), there were several elements at play when working toward fully automatic heart functional assessment of echocardiograms and automatic classification of their standard views hence developing different values in each parameter.[8] In addition to clutter, noise lowers the clarity of the images, thus limiting the ability to perform accurate view classification, (1) Physiological differences across participants, varying acquisition settings (angle, depth, scanning machine characteristics, foreshortening, etc.), and the sonographer's experience all contribute to intra-view variability of echocardiograms of the same cardiac view; (2) Identical information in both views (such as valve motion, wall motion, left ventricle, etc.), as well as poorly defined transducer location during collection, which may result in imprecise capture and confusing view, echocardiograms of various cardiac perspectives exhibit inter-view similarity; (3) Duplicated data, such as test details (examination date and time, ECG, heart rate, frame rate, and scanner details), which are present in all echocardiograms regardless of view, could taint the categorization procedure. Machine learning-based algorithms could reduce those shortfalls.[9]

The computational cost of our model is measured according to how much time it takes for the model to take the data from the input layer and gives the result on the output layer. We found that our model takes approximately ±0.1489 - 0.1906 seconds to predict a single sample of data. This prediction speed is also universally rapid, while normal examination would take around 15 to 60 minutes. Please note that this measurement does not include data acquisition from the pre-processing phase, and it ran on the following hardware:

- RAM 32 GB
- GPU: NVIDIA GeForce GTX 1080 Ti
- Processor: Intel (R) Core (TM) i7-6800K CPU @ 3.40GHz

Although there has been fully automated echocardiographic interpretation, which can automatically measure cardiac parameters (ejection fraction, LV mass index, and left atrial volume index), which has been widely used to assist in diagnosis, our study provides a different approach using sequential pattern memory of echocardiographic.[16] This tested machine learning algorithm proved fairly accurate and delivered relatively high sensitivity of echocardiogram videos compared to manual echocardiography calculation.

Additionally, as accurate interpretation of echocardiographic pictures may depend heavily on clinician expertise, performance performed by trained AI models may be superior to that of conventional, inexperienced doctors. Our approach, however, has the potential to be an effective prescreening tool for heart failure diagnosis because it is quick, accurate, and only reliant on 2AC, 4AC, and PLAX views. It also provides an automatic diagnostic workflow.

Study Limitation

This was a single-center study performed on patients with clinical indications for echocardiography. Even though the size of our test group can be considered negligible (128 patients) in the era of big data, the number of patients was sufficient to reach high levels of statistical significance compared with the reference technique. However, it is essential to note that this study may risk overfitting due to its small population. Extensive validation, preferably multi-center randomized controlled trials with a more significant number of patients, is required before they may be approved, reproducible, and generalizable for clinical use. In addition, combining multiple views to discriminate HF might help improve accuracy. Afterward, more studies to investigate the effect of clinical use of machine learning algorithms on patient outcomes. That being said, the prospect of high-performance computing may require significant financial investment and ethical clearance, yet it will reduce associated costs in the future.

Nevertheless, future studies with more significant numbers of patients and specific pathologies spanning a more comprehensive range of RV volumes and EF would be needed to confirm our findings further.

CONCLUSION

Method for automated categorization of HF and normal patients using a novel deep learning method called LIFES was presented. The proposed approach performs well in relation to manual echo by experts with high accuracy, sensitivity, and specificity rate. This study adds to the growing literature that ML-based algorithms can improve image interpretation efficiency and reliability and is the first of its kind to utilize LSTM to categorize HF and normal patients solely from echocardiography images. Further research is warranted to validate the method on a larger dataset and reduce bias. In the future, this method can be used in real-time in complete software that streams images directly from an ultrasound scanner. Hence, it can serve as a promising way to overcome challenges associated with current clinical workflow, streamline repetitive tasks, and provide preliminary interpretation in areas with insufficiently qualified cardiologists.

CONFLICT OF INTERESTS

The authors declare no competing interests and received no funding from any affiliations.

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Acute Limb Ischemia due to Arterial Thrombosis in a Patient with COVID–19 Pneumonia: A Case Report

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ABSTRACT

The COVID-19 pandemic has caused more than 4 million deaths worldwide to date. During the course of the COVID-19 pandemic, thrombotic complications due to hypercoagulable state have emerged as an important issue. Acute limb ischemia is one of emergency cases in vascular disease caused by a sudden decrease in arterial limbs perfusion. Here, we report a 53-year-old male patient with severe COVID-19 and a history of uncontrolled type 2 diabetes mellitus (T2DM) who developed extensive arterial thrombosis and limb ischemia despite being on therapeutic-dose anticoagulation, requiring surgical intervention. Right and left leg open thrombectomy was performed at day 7 after admission due to the excruciating pain and the worsening of the limb conditions. The patient was transferred to intensive care unit in emergency room because of the unstable hemodynamic and passed away a few hours after the surgery. For critically ill patients with COVID-19, special attention should be paid to abnormal coagulation dysfunction and microcirculatory disorders.

Keywords: *acute limb ischemia, ALI, COVID-19, diabetes mellitus, hypercoagulable state.*

INTRODUCTION

The respiratory disease from coronavirus disease 2019 (COVID-19) has caused over 230 million confirmed infections globally, including Indonesia, with over 4 million deaths as of September 2021.[1] Extra-pulmonary complications of COVID-19 are increasingly reported in the literature, including hypercoagulable state and thromboembolic events.[2]

Acute limb ischemia is one of emergency cases in vascular disease caused by a sudden decrease in arterial limbs perfusion. Patients with hypercoagulation state are at risk of arterial thrombosis. The decision of surgical intervention must be determined quickly in patients with hypercoagulation state due to the clinical outcome. Many studies had shown an overall increase in mortality and amputation rate in hospitals.[3]

We described a case of acute limb ischemia due to arterial thrombosis associated with hypercoagulable state in a patient with COVID-19 pneumonia. The aim of this report is to report our first experience managing such case from a clinicopathological conference.

CASE ILLUSTRATION

A 53-year-old male patient with past medical history of uncontrolled type 2 diabetes mellitus and hypertension came to Dr. Soetomo General Hospital in Surabaya, Indonesia during COVID-19 pandemic with shortness of breath and anosmia since 3 days before admission. Since 8 days before admission, he had experienced occasional dry cough and fever. Retroorbital pain, headache, and skin rash were absent. He had no problem with passing urine and bowel movement. There was history of close contact with his confirmed COVID-19 wife and son. History of COVID-19 vaccination was denied.

In the emergency room, he was alert. Temperature was 38°C, pulse 102 bpm, blood pressure 153/70 mmHg, respiratory rate 30 times/min, and pulse oximeter 86% saturation with 3 lpm nasal canulla supplemental oxygen. The chest, abdomen, and remainder of the physical examination was normal. He had a weight of 75 kg, height of 170 cm, and calculated body mass index (BMI) of 25.9%. Laboratory results revealed an elevated random blood glucose (294 mg/dL), elevated aspartate aminotransferase (89 U/L), elevated alanine aminotransferase (53 U/L), and elevated D-Dimer (1,094 ng/mL). Kidney function tests were normal (blood urea nitrogen 9 mg/dL and serum creatinine 0.71 mg/dL). The SARS-CoV-2 real time PCR examination showed positive results. Chest X-ray revealed bilateral pneumonia.

The patient was transferred to the isolation ward (day 2 of treatment) for further evaluation and treatment. He was given intravenous fluid with NaCl 0.9%, oxygen supplementation 6 lpm, Remdesivir 200 mg i.v q.d, Lovenox 40mg s.c b.i.d, Novorapid 12 unit s.c t.i.d, Lantus 26 unit s.c q.d, Dexamethasone 6 mg i.v q.d, Amlodipine 5 mg p.o. q.d, N-acetylcysteine 600 mg p.o. b.i.d and Curcuma 20 mg p.o. b.i.d. On the second day in isolation ward (day 3 of treatment), laboratory results showed neutrophilia (74%), lymphocytopenia (16%), elevated D-Dimer (1,760 ng/mL), elevated random blood glucose (369 mg/dL), elevated HbA1c (12.3%), elevated CRP (14.5 mg/dL), and elevated Ferritin (5,346 ng/mL). Liver function tests remain abnormal. He also underwent plasma IL-6 level test and an increase in IL-6 with a value of 11.04 pg/mL was found. Blood gas analysis showed a metabolic acidosis condition.

On the fourth day in isolation ward (day 5 of treatment), he developed bluish discoloration and worsening pain in both legs (**Figure 1**). His lower extremities were swollen and bluish in color, cold to the touch, and had a peripheral oxygen saturation of 75% (right foot) and 70% (left foot). The pulse of the right and left femoral artery, tibialis posterior artery, and dorsalis pedis artery were unpalpable bilaterally. He also still complained of difficulty breathing despite oxygen supplementation. Laboratory tests showed leukocytosis, with leukocyte value of 19,060 accompanied by increased Neutrophil Lymphocyte Ratio of 14.6 and elevated procalcitonin (3.78 ng/mL). Random blood glucose, liver function tests, and Ferritin remain high. D-Dimer was extremely elevated with D-Dimer value of 336,600 ng/mL.

Thromboelastography (TEG) assay was performed in this patient and the result showed increased coagulation activity, normal fibrinogen activity, normal platelet activity, and adequate fibrinolytic activity. TEG suggest hypercoagulability (enzymatic) factor (**Figure 2**).

He was consulted to the thoracic and vascular surgery department for thrombectomy. Preoperative doppler ultrasound was performed and showing thrombosis of left and right superficial femoral artery (**Figure 3**). Based on the examination, the patient was diagnosed with acute limb injury with modified Rutherford classification IIb. An emergency revascularization

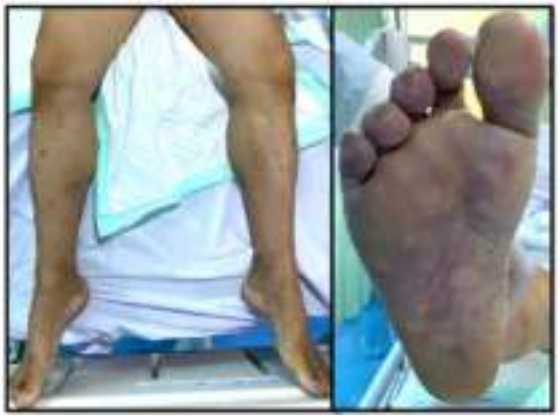

Figure 1. Showed ischemia in the patient's limbs on September 1st, 2021

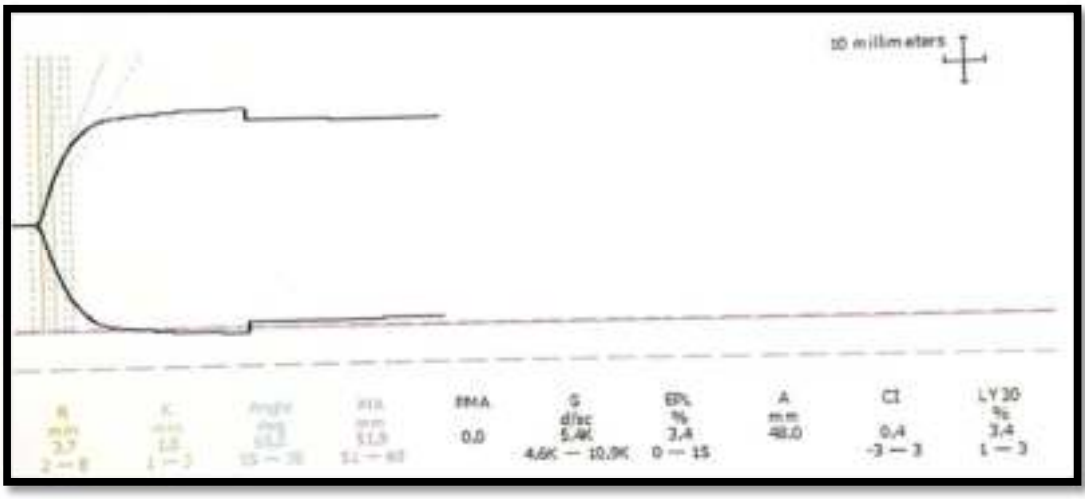

Figure 2. Thromboelastography (TEG) assay suggest a hypercoagulability (enzymatic) factor.

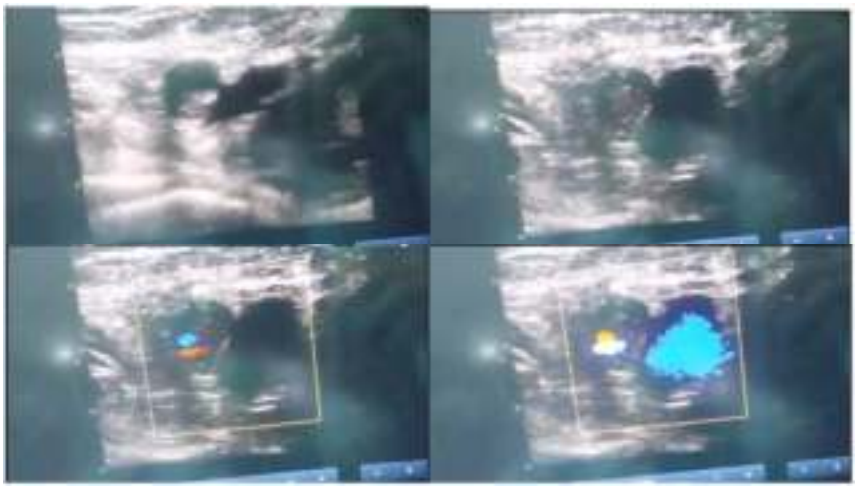

Figure 3. Doppler ultrasonography of left lower Limbs on September 1st, 2021 at Dr. Soetomo Hospital Surabaya indicated the presence of thrombus from left superficial femoral artery (filling>50% lumen).

with open thrombectomy procedure was suggested. However, the procedure was delayed due to the concern of the patient and his family. Oxygen supplementation was changed to 30 lpm high flow nasal canulla, anticoagulant was changed to Heparin 5000 unit i.v. o.d and Heparin 24.000 unit i.v. q.d, antibiotic Cefoperazone Sulbactam 1 gram i.v. q.i.d was added.

On the fifth day in isolation ward (day 6 of treatment), he presented with hematuria. Laboratory results showed prolonged PT (26.8 seconds) and APTT (97.1 seconds). Heparin was stopped due to hematuria and the preparation of thrombectomy procedure. Chest x-ray showed bilateral pneumonia with decreased infiltrates.

He underwent a thrombectomy on September 3rd, 2021. Preoperative laboratory results revealed a decrease in the value of PT (11.9 seconds), APTT (24.8) and D Dimer (23,990 ng/mL) compared to the previous day. Open thrombectomy procedure using Fogarty catheter was performed and thrombus of length 43 cm from the left leg and 40 cm from the right leg were removed (**Figure 4**). Post-operative evaluation was performed and the pulse of the right and left femoral artery, popliteal artery, tibialis posterior artery and dorsalis pedis artery were palpable bilaterally.

He was transferred to intensive care unit in emergency room after the procedure because of

unstable hemodynamics. He was still intubated and placed on a ventilator. Laboratory results revealed normochromic normocytic anemia (Hb 6.6 g/dL), leucocytosis (27.050/µL), thrombocytopenia (139,000/µL), hyperkalemia (6.5 mmol/L), hypocalcemia (8.1 mmol/L) and elevated lactic acid (9 mmol/L). Kidney function tests were abnormal (blood urea nitrogen 34 mg/dL and serum creatinine 1.7 mg/dL) and liver function tests were extremely elevated (aspartate aminotransferase 470 U/L alanine aminotransferase 783 U/L). Blood gas analysis showed worsening metabolic acidosis. Examination of serum ketones and urine ketones was not performed so that the possibility of diabetic ketoacidosis could not be ruled out.

Figure 4. Thrombus obtained from the total thrombectomy with a length of 40 cm and 43 cm (from right and left femoral artery respectively)

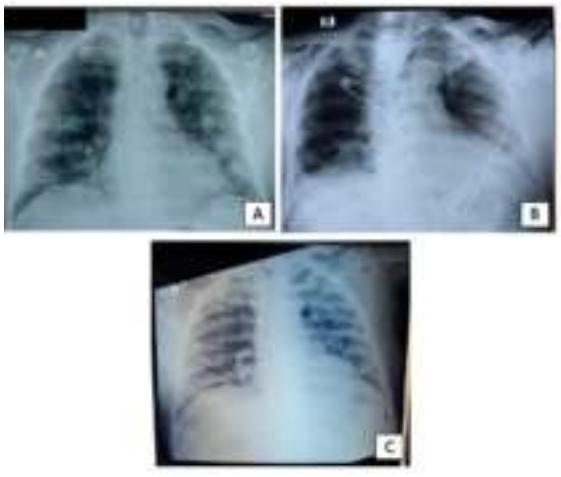

Figure 5. An overview of the development of chest x-ray during hospitalization from August 27, 2021 to September 3, 2021. A. Showed a bilateral pneumonia. B. Showed the improvement of patient's chest x-ray on September 2, 2021. C. Showed the worsening of patient's chest x-ray on September 3, 2021.

Chest x-ray showed bilateral pneumonia with increased infiltrates (The history of patient's chest x-ray results during hospitalization is shown in **Figure 5**). The patient passed away few hours after thrombectomy procedure.

DISCUSSION

In this case, we presented an unusual case of COVID-19 infection with an initial stable period and a rapid deterioration leading to ICU admission, and eventual demise due to extensive arterial thrombosis. As described by recent studies, patients with COVID-19 have an increased risk of both venous and arterial thrombotic events.[4,5] The pathophysiology is complex and not yet fully understood.

Previous study mentioned the symptoms of acute limb ischemia are as following: pain, numbness, paresthesia, coldness, and irreversible purpura at extremities.[6] In this case, the patient showed clinical symptoms in the form of pain, paresthesia and bluish rash accompanied by legs that were cold to touch.

Several studies indicate that severe COVID-19 infections are associated with higher D-dimer levels, reflecting a more pronounced hypercoagulable state.[7,8] In this case, the patient had an increased level of D-dimer (336,600 ng/mL). The thromboelastography assay results confirmed the hypercoagulable state in this patient. Based on the clinical conditions, it can be presumed that the hypercoagulation state with clinical ischemia in this patient signified severe illness and required close monitoring and appropriate early intervention management.

SARS-CoV-2 directly attacks vascular endothelial cells and activates the coagulation cascade after causing endothelial injury. This pathologic insult is suggested to result in excessive cytokine release and storm from activating of widespread coagulation factors while inhibiting fibrinolysis causing extensive thrombosis similar to disseminated intravascular coagulation. IL-6 is a key factor in SARS-CoV-2 induced inflammatory storm. While IL-6 can stimulate the liver to synthesize fibrinogen and thrombopoietin, it also upregulates the expression of vascular endothelial growth factor to disrupt the stability of vascular barrier and

stimulate monocytes to express more tissue factors, thereby activating the extrinsic pathway of coagulation.[9] These coagulation abnormalities along with elevated D-dimers are likely indicators for higher mortality predisposing the patients to a variety of ischemic and thrombotic events.[8]

This patient had the history of uncontrolled type 2 diabetes mellitus. During hospitalization there was elevated random blood glucose (470 mg/dL) and HbA1c (12.3%). A study by Calvisi et al. showed diabetes, hyperglycemia and glycemic variability were strong risk factors for the development of thromboembolic complications in COVID-19 patients. Diabetes was associated with both inflammation and coagulopathy (elevated C reactive protein and D-dimer levels, mild prolongation of the prothrombin time and decreased antithrombin III), suggesting that a hyperglycaemia-related amplification of the pathobiological mechanisms of immunothrombosis could be responsible of the increased thrombotic risk.[10] COVID-19 is a disease that can trigger hypercoagulable conditions, so that it can increase the incidence of ALI in patients with a history of T2DM. Viral infiltration causes a process of cell disruption, leading to a disseminated intravascular coagulopathy (DIC)–like clinical feature, in which D-dimer breakdown products and fibrin/fibrinogen are significantly increased, and microvascular microthrombi are formed.[11]

In this case, the patient underwent thrombectomy. Thrombectomy was indicated in accordance to this patient stage being Rutherford stage IIB.[12] According to the guideline, grade IIB ALI should undergo an emergency revascularization procedure within 6 h after the diagnosis has been made.[13] Unfortunately, the procedure was delayed due to the concern of the patient and his family. Prolonged ischemia can cause muscle cell liquefactive necrosis and K^+ ion, myoglobin, creatine kinase, lactic acid, and superoxide accumulation in the affected limb. These metabolites perfuse throughout the body upon revascularization and cause hyperkalemia, arrhythmia, pulmonary edema, metabolic acidosis, and myoglobinuria, and in severe cases, it can cause sudden death from heart and renal failure. The so-called ischemia–reperfusion injury is a severe complication that determines prognosis after the revascularization of ALI.[6] This ischemia–reperfusion injury could be the cause of death in this patient as we found hyperkalemia, worsening metabolic acidosis, elevated kidney test results, and elevated lactic acid after the thrombectomy procedure.

Open surgical techniques have been preferred because time to reperfusion is rapid especially when faced with class IIb ALI. Early operative intervention, however, result in considerable risk of perioperative mortality. Despite advances in resuscitative care, reports state mortality rates as high as 20% in patients undergoing operative revascularization for ALI.[14] A combined approach of mechanical and pharmacologic catheter-based techniques are becoming more prevalent as an alternative to more invasive and open surgical approaches that typically incur a higher morbidity and mortality, especially in patients with comorbidities.[13] Studies showed that intraoperative hyperglycemia will result in postoperative infections, cardiovascular and cerebrovascular accident, cognitive dysfunction, and other poor outcomes in diabetic patients. Effective glycemic management in patients with diabetes can improve their surgical outcomes.[15]

Several studies suggested that elevated aminotransferases is associated with higher mortality in COVID-19.[16,17] Multiple hypotheses such as direct viral cytotoxicity through ACE-2, drug-induced liver injury, immune-mediated damage, and passive congestion have been proposed.[18] The liver function tests of this patient were high upon the admission and got extremely elevated after the thrombectomy procedure. Systemic organ ischemia and hypoxia would occur in diabetic patients due to microvascular disorder. Related research shows that severe hypoxia results in increased metabolic activity of transaminases and bilirubin metabolism disorders in the hepatocytes, and even liver necrosis.[19] Operative blood loss, ischemia, and stress will aggravate the state of systemic organ ischemia and may be the reason for the further transaminase increase in the diabetic patients postoperatively.

CONCLUSION

ALI accompanied with COVID-19 and type 2 Diabetes mellitus is a complex case. It requires comprehensive COVID-19 treatment, good management of glycemic control and immediate salvage limb treatment. The ischemia–reperfusion injury can be a cause of death in COVID-19 patients with limb ischemia undergoing thrombectomy. The prognosis for ALI with COVID-19 and T2DM is worse than in other patients and most cases ended with death. Further studies is needed to establish the optimal management of ALI with COVID-19 and T2DM.

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Hemoperfusion as an Adjuvant Therapy in Maintenance Hemodialysis Patients with Severe COVID-19: A Single Centre Experience

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ABSTRACT

Mortality rate among maintenance hemodialysis (HD) patients with COVID-19 is alarmingly high. In Fatmawati Hospital, most of HD patients with COVID-19 presented with acute respiratory distress syndrome (ARDS). Hemoperfusion (HP) is a blood purification therapy used to remove cytokines and inflammatory mediators to prevent ARDS worsening and organ failure. We report 6 cases of COVID-19 in maintenance HD patients. HP and HD were performed in two consecutive days when patient developed early ARDS as indicated by inflammatory markers elevation. HP and HD were conducted by using resin-containing cartridge and high-flux dialyzer, respectively, for 4 hours. Improvements in CRP levels, PaO_2/FiO_2 ratios, and chest X-rays were observed after 2 sessions of HP in most of our patients. Based on our clinical experience, the timing of HP delivery is critical and should be undertaken in the early phase of ARDS, but larger studies are still needed.

Keywords: *hemoperfusion, hemodialysis, COVID-19, cytokines, resin.*

INTRODUCTION

COVID-19 mortality among hemodialysis (HD) patients in Fatmawati Hospital, Jakarta, Indonesia, has been found to be higher than among non-dialysis patients, and most of HD patients with COVID-19 have acute respiratory distress syndrome (ARDS). Hemoperfusion (HP) is a blood purification therapy that is used to remove cytokines and inflammatory mediators to prevent worsening of ARDS and organ failure.[1–3] In our hospital, HP is performed with resin-containing cartridges in HD patients with severe COVID-19 when their clinical condition and inflammatory markers are worsening. We assess room air oxygen saturation, PaO_2/FiO_2 ratios, and C-reactive protein (CRP) levels to determine the severity of the disease. We present a case study of 6 maintenance HD patients with ARDS who were admitted to our hospital and treated with hemoperfusion.

CASE ILLUSTRATION

Six maintenance HD patients with COVID-19 were admitted to our hospital and treated with hemoperfusion between September 2020 and January 2021.

Case 1

Female 42 years old came with shortness of breath, cough, and fever for 2 days. She had been on maintenance dialysis for 25 months due to diabetes. Blood glucose was controlled with oral hypoglycemic agent and during hospitalization insulin was initiated. She also had coronary artery disease with history of PCI. She came with pO2 124 with non rebreathing mask 10 L/min and high CRP 30.7 mg/dl. She underwent intermittent hemodialysis during hospitalization. On day 16, she was desaturated with PaO2/FiO2 114 and CRP 19.8 mg/dl. Hemoperfusion was initiated on day 17. After second hemoperfusion, PaO2/FiO2 was increased, and CRP decreased to 7 mg/dl. She was discharged from high care unit to ward on day 22.

Case 2

Female 44 years old came with shortness of breath and cough for 2 days. She had been on maintenance hemodialysis for 5 years due to staghorn kidney stones and residual kidney function of 50 ml. She was admitted with PaO2/FiO2 150 and received high flow nasal cannule 60LPM/FiO2 80%. She came with CRP 2.1 mg/dl. On day 5, she was desaturated with PaO2/FiO2 130 and elevated CRP 32 mg/dL. Hemoperfusion was initiated on day 5. After second hemoperfusion, PaO2/FiO2 was increased to 256 and CRP decreased to 1.1 mg/dl. She was discharged home on day 12.

Case 3

Male 67 years old, came with cough for 4 days. He had been on maintenance hemodialysis for 8 months due to type 2 diabetes. He had coronary artery disease with no history of PCI. He was somnolent with PaO2/FiO2 ratio 206 and being given NRM 10LPM. At admission, CRP was 3 mg/dl. On day 5, PaO2/FiO2 was decreased to 141 and CRP was elevated to 26.9 mg/dl. Hemoperfusion was initiated on day 5. After second hemoperfusion, PaO2/FiO2 ratio was elevated to 318 and CRP was decreased to 4.7 mg/dl. On day 12 he developed sepsis with fever, increased procalcitonin to >32 ng/ml, and blood culture showed *Klebisella pneumoniae*. Despite antibiotic escalation, on day 15, the patient's clinical condition worsened, and he was intubated. He went into septic shock, and his procalcitonin level remained high. He succumbed to the disease on day 17.

Case 4

Male 62 years old came with fever and cough for 2 days. He was on maintenance hemodialysis for 71 months due to type 2 DM. On admission, CRP was 19.9 mg/dl. On day 3, he was desaturated to 94% on NRM 15 LPM. Then he received HFNC FiO2 70% flow 50 LPM. CRP was elevated to 24 mg/dl and IL-6 was 32.8 pg/ml. Hemoperfusion was initiated on day 3. After second hemoperfusion, shortness of breath was reduced, PaO2/FiO2 ratio was increased to 240, CRP and IL-6 was decreased to 11.8 mg/dl and 17.6 pg/ml respectively. He was discharged on day 16.

Case 5

Female, 31 years old, came with shortness of breath, fever, and malaise for 10 days. She was on maintenance hemodialysis for 67 months due to chronic glomerulonephritis. On day 5, she was desaturated to 70% on HFNC FiO2 90% flow 60 LPM. CRP was elevated from 4.6 mg/dl to 7.1 mg/dl and IL-6 was 35.9 pg/ml. Hemoperfusion was initiated on day 5. After first hemoperfusion, PaO2/FiO2 ratio was slightly elevated to 101 but then after second hemoperfusion it was decreased to 66. Although CRP and IL-6 was decreased after second hemoperfusion, she succumbed to the disease on day 8 due to respiratory failure and disseminated intravascular coagulation.

Case 6

Male, 41 years old, came with shortness of breath and cough for 4 days. He was admitted right after finishing hemodialysis in other hospital. He came with PaO2/FiO2 90, CRP 11.8 mg/dl, IL-6 20.6 pg/ml. Hemoperfusion was initiated on day 1. After second hemoperfusion, PaO2/FiO2 was elevated to 192, CRP and IL-6 was decreased to 6 mg/dl and 5 pg/ml, respectively. He was discharged to ward on day 10.

All patients received standard of care i.e. oseltamivir 30 mg after every HD session, unfractionated heparin, empirical antibiotic, acetylcysteine, and intravenous dexamethasone 6 mg QD. Case 1-5 received intermittent hemodialysis during hospitalization to achieve euvolemia. Ultrafiltration was performed to

achieve their dry weight. Case 6 was admitted to our hospital after finishing hemodialysis session in other hospital. All patients had ARDS with euvolemic state when underwent HP. HP was performed using HA-330 resin-containing cartridges (Jafron Biomedical Company, China). To wash the extracorporeal circulation tubing and HP cartridges, 2000 ml of 0.9% NaCl and 12,500 units of heparin were used.

The patients underwent HP concomitantly with HD using a Surdial™ 55 Plus machine (Nipro, Japan) with the high-flux dialyzer Elisio™ 13H. Heparin was injected as an anticoagulant agent throughout HD via the arterial line at 10–20 IU/kg/h depending on the patient's coagulation status. The blood flow rate was 200–300 ml/minute and the dialysate flow rate 500 ml/minute. Each session was performed for 4 hours. A second course of HP was performed 24 hours after the first.

The PaO_2/FiO_2 ratio in all the patients improved after the first HP, but only 5 patients showed further improvement after the second HP. The PaO_2/FiO_2 ratio of case 5 deteriorated after the second HP (**Figure 1**). The CRP levels of 4 patients improved after the first HP, and 5 patients had improved CRP levels after the second HP. Case 5 developed increased CRP levels after the second HP (**Figure 2**). Serial chest X-ray after second HP showed improvement, except for case 5.

Facilities to determine interleukin-6 (IL-6) levels were not available in our hospital in the early phase of the COVID-19 pandemic. IL-6 tests were therefore only performed for the last 3 patients, all of whom showed lower levels after the first and second HPs (**Figure 3**).

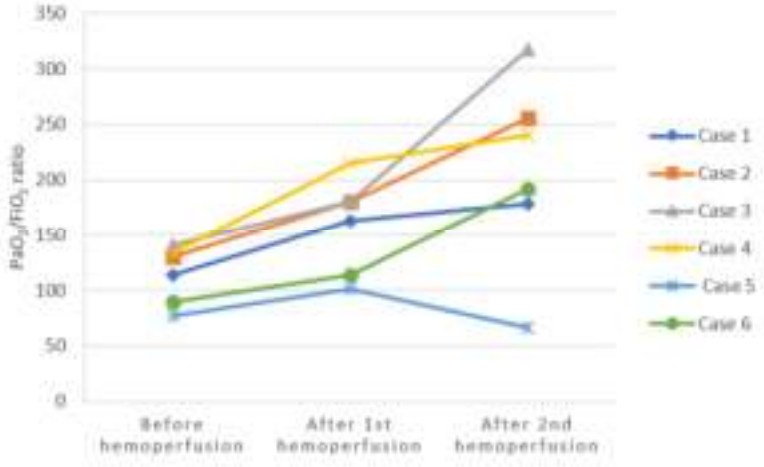

Figure 1. Serial PaO_2/FiO_2 ratio before and after hemoperfusion.

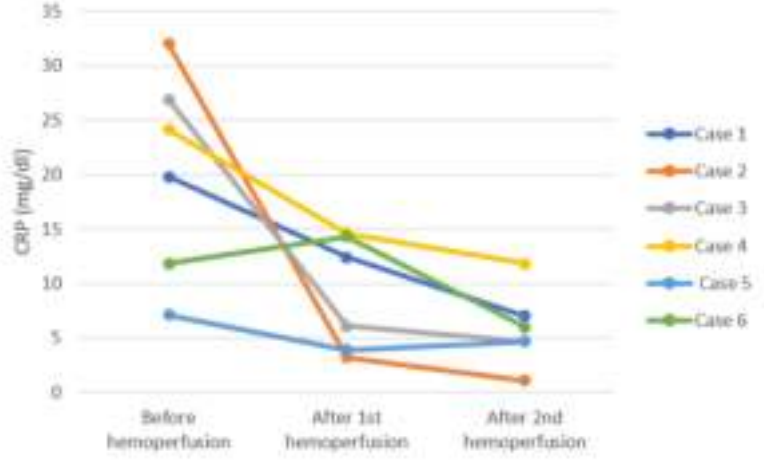

Figure 2. Serial CRP level before and after hemoperfusion.

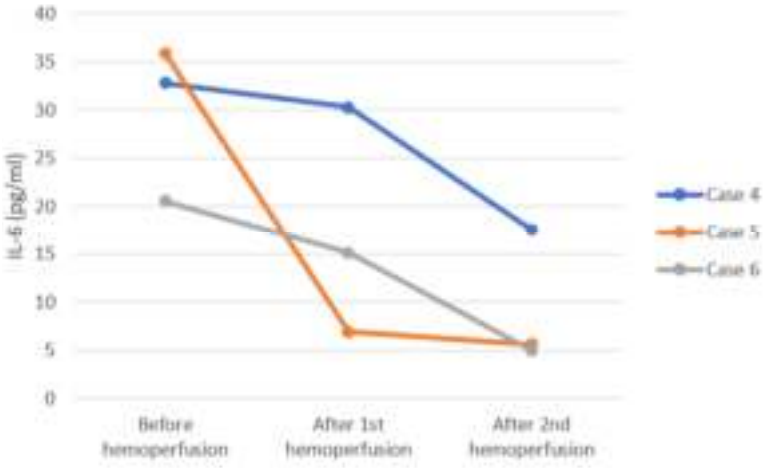

Figure 3. Serial IL-6 before and after hemoperfusion.

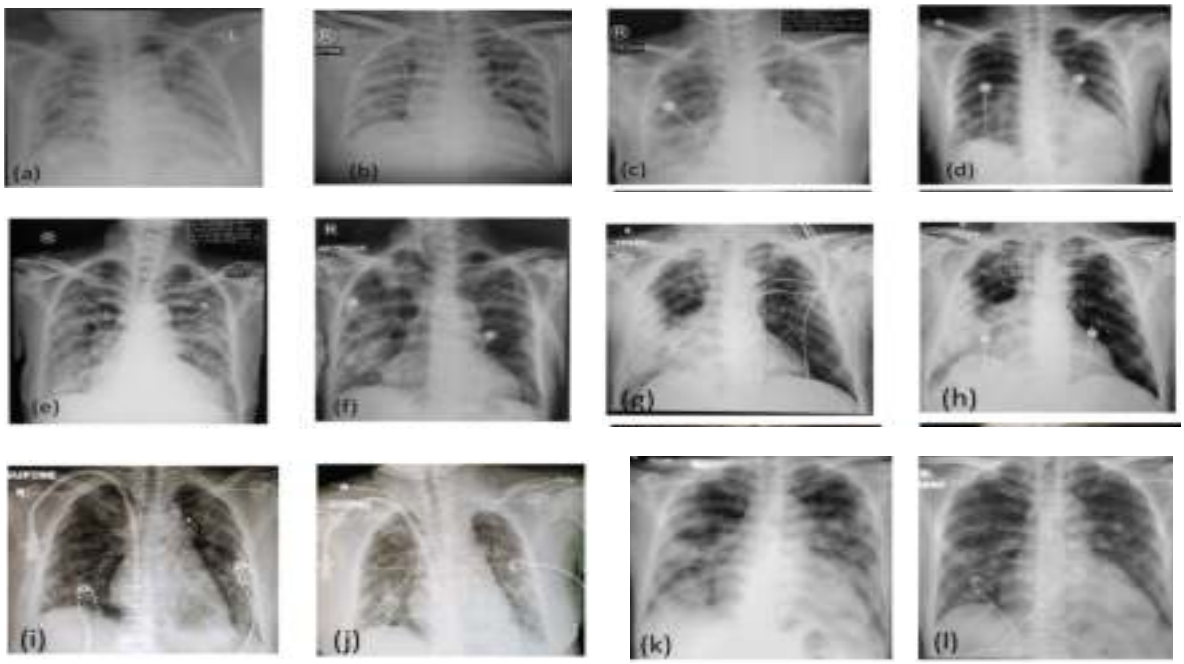

Figure 4. Serial chest X-ray before and after hemoperfusion.
Left: before HP, Right: after second HP
(a),(b) Case 1; (c),(d) Case 2; (e),(f) Case 3; (g),(h) Case 4; (i),(j) Case 5; (k),(l) Case 6

DISCUSSION

Cytokine storm is one of the contributing factors leading to ARDS. Three of the most important proinflammatory cytokines of the innate immune response are IL-1, TNF-α, and IL-6. In COVID-19, a cytokine storm results from a sudden acute increase in circulating levels of pro-inflammatory cytokines and leads to acute lung injury and a more severe form of ARDS, which is a major cause of mortality in this disease.[4] Emerging evidence has indicated the potential benefits of managing this cytokine storm to prevent severe ARDS and mechanical ventilation.

Extracorporeal blood purification has been proposed as one of the treatments to remove pro-inflammatory cytokines and could potentially be beneficial in severe COVID-19.[1–3,5] HP is a blood

Table 1. Baseline characteristics.

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Female	Male	Male	Female	Male
Age (years)	42	44	67	62	31	41
Glasgow coma score	15	15	14	15	15	15
Hemoglobin (g/dl)	9.3	8.5	9	9	10.9	7
Leucocyte (/μl)	8100	1100	10300	5900	4200	3800
Thrombocyte (x10^3/μl)	343	340	160	191	123	210
ALC (/μl)	729	88	1030	413	588	760
NLR	9.3	10.5	8.7	12.1	5.7	3.5
CRP (mg/dl)	30.7	2.1	3.0	19.9	4.6	11.8
Procalcitonin (ng/ml)	5.4	>32	4.11	1.2	2.16	31.4
d-dimer (ng/ml)	3040	850	3814	2040	1520	4360
Lactate (mmol/l)	1.2	1	1.4	0.7	2.4	2.8
Glucose (mg/dl)	150	90	120	125	84	83
AST (U/l)	35	40	29	32	21	43
ALT (U/l)	33	32	23	35	10	25
Ureum (mg/dl)	190	120	150	157	124	218
Creatinine (mg/dl)	7.5	5.4	6.7	15.5	10.8	18.5
Oxygenation	NRM	HFNC	NRM	HFNC	HFNC	HFNC
PaO2/FiO2 ratio (mmHg)	155	150	206	134	77	90
Hemodialysis vintage (months)	25	60	8	. 71	67	36
Residual urine volume (ml)	600	50	800	50	50	500
mSOFA score	7	8	8	8	9	8
Dialysis access	AVF	AVF	AVF	AVF	CDL	AVF
Symptoms onset to admission (days)	2	2	4	2	10	4
Admission to hemoperfusion (days)	17	5	5	3	5	1
Diabetes mellitus	Yes	No	Yes	Yes	No	No
Hypertension	Yes	Yes	Yes	Yes	No	Yes
Coronary artery disease	Yes	No	Yes	Yes	No	Yes
Mortality	No	No	Yes	No	Yes	No

NRM: non-rebreathing mask; HFNC: high flow nasal cannule; AVF: arterio-venous fistula; CDL: double lumen catheter

purification therapy that was introduced in the early 1960s to increase HD efficiency in reducing uremia. During HP, blood passes through a cartridge containing a sorbent material, and a physicochemical process allows the material to retain specific molecules. HP has also been used to treat drug and chemical intoxication and fulminant hepatic encephalopathy.[6] Its indications have further expanded to include the treatment of acute inflammatory conditions such as sepsis, pancreatitis, and acute lung injury.[7–9]

In our experience, we used HP in patients with ARDS and elevated serial C-reactive protein (CRP) levels. ARDS is diagnosed when patients with confirmed diagnosis of COVID-19 meet the Berlin 2012 ARDS diagnostic criteria of (i) acute hypoxemic respiratory failure; (ii) presentation within 1 week of worsening respiratory symptoms; (iii) bilateral airspace disease on chest X-ray or computed tomography (CT); and (iv) acute hypoxemic respiratory failure without cardiac failure as the primary cause. The severity of ARDS is defined as mild (200 mmHg < PaO_2/FiO_2 ≤300 mmHg), moderate (100 mmHg < PaO_2/FiO_2 ≤200 mmHg), and severe (PaO_2/FiO_2 ≤100 mmHg).[10] Among the 6 patients in this report, 2 had severe ARDS, 3 had moderate ARDS, and 1 had mild ARDS.

HP is a blood purification modality that can be performed alone or in conjunction with other modalities such as HD, continuous renal replacement therapy (CRRT), and extracorporeal membrane of oxygenation (ECMO). HP with resin-containing cartridges in combination with CRRT and ECMO has been reported to be beneficial in increasing SpO_2, decreasing IL-6 and CRP, and preventing intubation.[11–14] HP alone has also been shown to provide good results in a few case reports.[15,16]

The sorbent material in the HP cartridge

comprises activated carbons (charcoal), ion-exchange resins and/or non-ionic resins. HA-330 cartridges contain neutro-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymers with loading capacity of 330 ml. The average diameter of the resin beads is 0.8 mm, and the pore size distribution is 500 Da–60 kDa. The resin beads can remove medium-sized molecules such as cytokines and complements with a molecular weight ranging from 10–60 kDa.[17]

In this study, the timing of HP played a critical role in providing an optimal outcome. The HP timing for case 1 was quite different from that of the other cases. Case 1 initially had a high CRP level. During close daily observation, her clinical and CRP levels improved with standard of care. However, we found elevated CRP levels and a worsening condition on day 17. This suggested systemic cytokine release and provided perfect timing for cytokine and inflammatory mediator removal. In cases 2, 3, and 5, increased CRP levels and worsening clinical conditions were observed on day 5, so HP was performed earlier than case 1. This finding suggests that it is crucial to observe inflammatory markers in COVID-19 patients together with their clinical condition to detect early increases in the markers and early worsening of their condition.

Among cytokines, IL-6 is a biomarker for disease severity and mortality. As we did not have facility to check real-time IL-6 at early phase of pandemic, we are only able to check IL-6 in 3 last cases. In those cases, IL-6 were decreased after first and second HP. This finding is in line with other case report, which also found improved levels of inflammatory parameters.[16]

All the patients except case 5 showed significant PaO_2/FiO_2 ratio improvements. Case 5 was the youngest of the 6 patients and had no other comorbidities, yet she did not survive. She developed severe ARDS when admitted and immediately received high-flow nasal cannula. She showed an improvement in SpO_2 until day 4 and worsened on day 5. Her CRP levels before HP were lower than in the other patients, and her improvement after HP was unlike that of the other patients. This may have been caused by the advanced stage of the disease as her symptoms had developed 10 days prior to hospital admission, and fibrosis had likely already occurred. She had the longest symptom onset and the highest modified sequential organ failure assessment (mSOFA) score among the patients. She developed respiratory failure and severe disseminated intravascular coagulation (DIC) before succumbing to the disease. Similarly, in one serial case report involving 4 COVID-19 patients in Iran, HP did not produce a significant therapeutic effect[18]. This could have been because HP was performed in the late stage of the disease as all the patients in the study had already been intubated. Performing HP in the late course of the disease may therefore result in a poor outcome even though it reduces CRP and IL-6 levels.

It has been suggested that HP be performed in a 2-1-1 order, that is, 2 cartridges in the first 24 hours and 1 cartridge for the following two days.[2] Due to the limited availability of cartridges in our hospital, we assessed the need for HP individually for each patient by evaluating the PaO_2/FiO_2 ratio and CRP level after each HP to determine the disease severity and inflammatory status. In most cases, we found improvements in PaO_2/FiO_2 ratios, CRP levels, and chest X-rays after the second HP, so we did not continue to third HP.

CONCLUSION

Improvements in CRP levels, PaO_2/FiO_2 ratios, and chest X-rays were observed after 2 sessions of HP in most of our patients. Based on our small clinical experience, the timing of HP delivery is critical and should be considered to be undertaken in the early phase of ARDS. We still need larger studies with control group to show best time of performing hemoperfusion, how many sessions are needed, and how its effect on mortality.

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Anal Swab in COVID-19 Patients

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ABSTRACT

In 2020, a new type of coronavirus (SARS-CoV-2) whose disease is called Coronavirus disease 2019 (COVID-19) has been reported. This virus was first discovered in Wuhan, China and has infected 90,308 people per March 2, 2020. As of the end of October 2020, more than 40 million people have been infected, with the death toll reaching 1,150,000 worldwide. Apart from respiratory tract infections, patients infected with this virus may exhibit other symptoms, such as diarrhea, abdominal pain, nausea, or vomiting. This means that the virus can be found in feces and anus, hence the anal swab can be used as a diagnostic tool for COVID-19 infection. The results of the specimen test show that the sensitivity of the nasopharyngeal swab positive detection rate is the highest and remains the gold standard for diagnosis. This sensitivity can also be influenced by the course of the disease that can infect the gastrointestinal tract so that anal PCR is performed for the diagnosis to detect the COVID-19 virus in patients.

Keywords: *Coronavirus; COVID-19, Pneumonia, Gastrointestinal disease, Anal swab.*

INTRODUCTION

The Coronavirus Disease (COVID-19) has spread widely in China and more than 190 other countries around the world. In 2020, more than 40 million people have been infected, with the death toll reaching 1,150,000 worldwide.[1,2] Apart from respiratory tract infections, patients infected with this virus may exhibit other symptoms, such as diarrhea, abdominal pain, nausea, or vomiting.[3,4] On March 20, 2020, WHO declared COVID-19 a pandemic.[5] As of March 24, 2021, there were 166,860,081 confirmed cases and 3,459,966 deaths worldwide. In Indonesia, 18,388 positive cases of COVID-19 and 142,952 deaths have been reported.[6,7] COVID-19 can be diagnosed by assessing patients' clinical condition as well as X-ray results of the lungs, and then confirmed using a PCR test.[8] PCR examination with nasopharyngeal and oropharyngeal swabs is the gold standard for diagnosing COVID-19.[9] In some cases not detected by PCR test, anal swab PCR test can be done as an alternative.[10] The following is a case report of anal swabs at a COVID-19 referral hospital. Anal swab was chosen as an evaluation for patients with gastrointestinal symptoms who also have COVID-19 symptoms. Anal swab is chosen to evaluate patients if the results of the nasopharyngeal swab are negative.

CASE ILLUSTRATION

Case 1

The patient is a female patient aged 81 years who had black stools for a week, with the onset of black stools 3-4 times a day and the most severe being in the last two days. Previously, the patient had a medical check-up at HGA Hospital and had received a PRC transfusion, with laboratory results of Hb 8.9, WBC 5,900, 171,000, and Hb 9.3 when examined in the ER. The patient had no comorbidities. An examination was carried out in the ER with the results as follows: blood pressure 122/77 mmHg, HR 83 beats/minute, respiratory rate 19x/minute, temperature 36.8° Celsius; the patient was diagnosed with probable COVID-19. An anal swab was performed (21/05/2020) with negative result and this was confirmed by PCR test. The results of the nasopharyngeal and oropharyngeal swabs (02/06/2020) were both negative. In addition, a chest X-ray was taken, showing a minimal infiltrate in the right lung and suggestive of pneumonia.

Case 2

A 59-year-old female patient presented with complaints of black stools for four days, Congestion (+), Heartburn (+), stomach feels full, and weight loss of 13 kg in a year. The patient did not experience fever, cough, runny nose, sore throat, and impaired smell. The patient was previously diagnosed with pulmonary TB and had been treated with Antitubercular Medications & SIDA since April 2020, but not yet received ARV treatment. History of HT, DM, heart disease, and asthma was denied. No drug allergies. An examination in the ER obtained the following results: blood pressure 114-72 mmHg; HR 87-95 beats/minute, strong; CRT <2 seconds. Several swabs were carried out with the results as follows: anal swab (4/06/2020): negative; anal swab (21/05/2020): negative; anal swab PCR test (31/05/2020): negative; and nasopharyngeal and oropharyngeal swabs PCR test (10/06/2020): negative. In addition, a chest X-ray was taken (18/05/2020), showing pneumonia with differential diagnosis of pulmonary tuberculosis. Meanwhile, heart size was within normal limits. The patient was diagnosed with probable COVID-19.

Case 3

A 50-year-old male patient came with a complaint of fever for ten days, with the highest temperature of 39.3°C. The patient had taken paracetamol and undergone temperature therapy at home. Cough (+), runny nose (-), phlegm difficult to come out, drinking water > 1.5 liters/day. Urine not overflowing, dripping

Table 1. Case illustration.

No.		Case 1	Case 2	Case 3
1.	Primary diagnosis	Probable COVID-19	Probable COVID-19	COVID-19 ARDS
2.	Secondary diagnosis	Anemia ec Melena	Anemia ec melena & chronic disease	Septic shock Hypertension
3.	PCR test	nasopharyngeal and oropharyngeal swabs (25/05/2020): negative nasopharyngeal and oropharyngeal swabs (04/06/2020): negative	nasopharyngeal and oropharyngeal swabs (10/06/2020): negative	
4.	Anal swab	Anal swab (21/05/2020): negative	Anal swab (31/05/2020): negative Anal swab (4/06/2020): negative	Anal swab (29/04/2020): positive SARS-Cov-2
5.	Roentgen	Infiltration and consolidation	Infiltration and consolidation	Infiltration and consolidation
6.	Electrocardiogram	Normal	Normal	Normal
7.	CT scan	-	Ground glass opacity	-

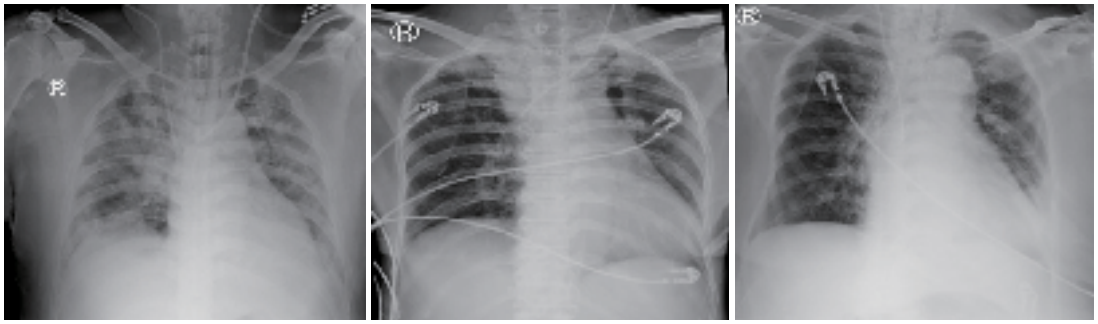

Figure 1. Result showing signs of worsening pneumonia.

with diarrhea for two days, frequency >5x/day. Decreased appetite. Examination in the ER obtained results as follows: systolic blood pressure: 106 mmHg, diastolic BP: 59 mmHg, respiratory rate: 40x/minute, temperature: 37.8° C, weight: 96.40 kg, height: 170 cm, HR: 91 beats/minute. A chest X-ray was taken with the results of suprahilal, perihilar, and pericardial infiltrates of both lungs, DD/Pneumonia, and pulmonary edema. Furthermore, an anal swab was performed on 29/04/20; the result was positive for SARS-Cov-2. Therefore, the patient was diagnosed with COVID-19 ARDS.

DISCUSSION

Based on the results of biopsies of gastric, duodenal, and rectal epithelial cells, SARS-CoV-2 has been shown to infect the gastrointestinal tract. This virus can be detected in feces; in 23% of patients, it was still found in feces even though it was not detected in respiratory samples.[11] This is in line with the third case of this case report which tested positive on anal swab. The collection was carried out at the time of onset, i.e., on the 3rd-7th day from hospital admission. This fact strengthens the suspicion of the possibility of fecal-oral transmission. In addition to being found in fecal specimens, the SARS-CoV-2 virus can also be identified using an anal or rectal swab. Upon further evaluation, the rectal swab ranks second in the positive detection rate.

The pathogenesis of SARS-CoV-2 remains unusual, but it is suspected that it is not much different from the more widely known SARS-CoV pathogenesis. In humans, SARS-CoV-2 primarily infects cells in the airways lining the alveoli. Protein S is reported to be a significant determinant in viral entry into host cells. The entry of SARS-CoV into cells begins with the fusion of the viral membrane with the plasma membrane of the cells. In such cases, an increase in CD38+HLA-DR+ T cells (activated T cells), especially CD8 T cells, was observed on the 7th-9th days of the nasopharyngeal and oropharyngeal swab examinations.[12-14] Regarding the first and second cases in this report, the results of the swabs were negative since the time of collection had already passed the incubation period of the virus in the oropharynx. However, the adverse effects were associated with other supporting examinations such as laboratory results and chest X-ray results. Both patients of these cases had pneumonia, thus being categorized as probable cases.

There was an increase in antibody-secreting cells (ASCs) and cold blood T follicular helper (Tfh) cells on the 7th day; this onset occurred before symptoms. A progressive increase in SARS-CoV-2 IgM/IgG was also found from the 7th day to 20th day in the gastrointestinal tract.[15] In the third case, the time of collection was influenced by the onset and the availability of reagents at the referral hospital. The change in sensitivity persisted for up to 7 days after symptoms relieved. In the humoral immune response, IgM and IgG are formed against SARS-CoV. IgM against SARS-CoV is lost by the end of the 12th week, while IgG can persist in the long term. The results of a prior study on patients recovered from SARS show that CD4+ and CD8+ memory T cells were specific for SARS-CoV after four years, but their numbers decreased.[16]

Table 2.

	Nasopharynx	Oropharynx	Intestine	Anal
Incubation	69 days	7-14 days	7-10 days	7-10 days
Detection presentation	16 % - 61.5 %	16%- 61.5 %	23%-24 %	23%-24 %

This case report collected various specimens from COVID-19 patients with the course of disease of 7 to 30 days, including specimens taken from nasopharyngeal and anal swabs, saliva, blood, and urine. PCR was used for nucleic acid detection and absolute counting of these specimens. Meanwhile, ELISA test was performed to detect anti-N IgM/IgG and anti-S-RBD IgG in serum samples of the patients.[17] The results of the tests on nucleic acid specimens showed the highest positive detection rate for nasopharyngeal swabs at 7-20 days and the highest average number of virus was found in the oropharyngeal swabs.

Case reports indicate that viral infections can enter the gastrointestinal tract. In the advanced stages of the disease, the virus can be detected on anal swabs, and the results remain positive even after nasopharyngeal swabs show negative results. This phenomenon, and the relatively high positive detection rate of anal swabs, reached 24% at the 14th–20th days. A previous study has found that the positive detection rate of saliva specimens is high, up to 61.5%. In addition, the study proved that viral nucleic acids were detectable in posterior oropharyngeal saliva specimens.[18] A better percentage of favorable agreement was observed in samples obtained within seven days of symptom onset. Nevertheless, the positive detection rate of saliva specimens in the study was only 16%, which presumably related to the sampling method. False-negative results on virological tests can occur due to the poor quality of collection or specimen management, specimen collections in the early stage of infection, or technical difficulties in the laboratory. Therefore, a negative result does not rule out the possibility of SARS-CoV-2 infection, especially in patients with a high index of suspicion. This is also in connection with the availability of reagents as well as the day of specimen collection.

Collection and transportation of nasopharyngeal swabs, anal swabs, saliva, blood, and urine specimens were stored at 4° C until use. The sampling methods are as follows:

1. Nasopharyngeal swab
2. Anal swab
3. Saliva

The results of this case study show that the nasopharyngeal swab is the best method for detecting SARS-CoV-2. Adverse effects occurred in the first and second cases because the samples were taken at intervals of 10 days and 11 days after the onset of symptoms. Meanwhile, the third case tested positive on anal swab since the sampling was carried out at the beginning of the course of disease, namely on the 3rd and 7th days. This is also influenced by the method used to take the specimen, the availability of reagents, and the form of tube transportation. Furthermore, the results of this study also suggest that nucleic acid testing for recovered patients should be carried out on nasopharyngeal swabs and other specimens to obtain a more accurate diagnosis of complete recovery from coronavirus infection when using nasopharyngeal and oropharyngeal swabs.

CONCLUSION

In these three cases, anal swab was carried out with gastrointestinal patients who also suspected with COVID-19. In cases with positive anal swab results, positive results were found after 10 days of symptoms (early phase) faster than the previous case study which shown that positive results for anal swabs shown after 14-20 days of symptoms (late phase).

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High Dose Oestrogen in Life Threatening Obscure Gastrointestinal Bleeding

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ABSTRACT

Obscure gastrointestinal bleeding is defined as recurrent or persistent gastrointestinal bleeding in the setting of normal upper and lower endoscopies. There are reported use of numerous pharmacological agents to halt the bleeding, including oestrogen. We report a case of middle age gentleman with multiple comorbidities, presented with life threatening gastrointestinal bleeding. He underwent bidirectional endoscopies and mesenteric angiogram, but failed to localise the bleeding. Red blood cell scintigraphy showed numerous bleeding points in small and large bowels. A 5-day oral high dose oestrogen was prescribed in view of difficulty to manage the bleeding, in which the hemostasis was ultimately achieved.

***Keywords*:** *Angiodysplasia, hormonal therapy, oestrogen, obscure gastrointestinal bleeding.*

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent gastrointestinal bleeding in the setting of normal upper and lower endoscopies. It can manifest as overt bleeding with visible passage of blood or occult bleeding which manifest as iron deficiency anaemia or positive faecal occult blood test.[1] It usually arises from small bowel with varying nature, ranging from angiodysplasia, Dieulafoy lesion to Meckel's diverticulum. Despite the advancement of small bowel endoscopy and video capsule endoscopy, 25% of patients may still have unidentifiable source of bleeding.[1] Besides, despite identification of source of bleeding, some of these patients may not be amenable for therapeutic endoscopic or surgical intervention due to severe comorbidities. In this group of patients, medical therapy may be considered to ameliorate the bleeding.

CASE ILLUSTRATION

A 63-year-old gentleman presented to us with a 3 days history of haematemesis and melaena. He was on double antiplatelet agents from recent myocardial infarction and coronary angioplasty. Other comorbidities included end stage renal failure, hypertension, dyslipidemia, and non-cirrhotic chronic hepatitis C. On examination, vital signs were unremarkable and per rectal examination revealed stale melaena. Laboratory investigations showed haemoglobin of 7.4 g/dL and platelet of 220 x 10^9/L, with normal coagulation profile.

Antiplatelet agents were withheld, and he was started on intravenous bolus esomeprazole 80mg followed by 8mg/hour infusion. Two units red blood cells were transfused. Oesophagogastroduodenoscopy (OGD) showed Forrest 2c ulcer at prepyloric region, however no varices and active bleeding was seen. On

the next day, he still passing out melaena. Repeated OGD was unremarkable. Subsequent computed tomography of mesenteric angiogram (CTA) failed to show any evidence of arterial bleeding. Colonoscopy was performed and showed oedematous ileocaecal valve with right sided diverticulosis, without active bleeding. Intubation into the terminal ileum was failed due to the oedema. Video capsule endoscopy was deemed not feasible due to concern of trapped capsule.

He was managed conservatively with blood transfusion until the day 7 of admission, when he developed another melaena with hypovolemic shock, requiring fluid/blood resuscitation and vasopressor. After initial stabilization, CTA was repeated but reported as unremarkable. Thus, he underwent a Tc-^{99m}-red blood cell scan which eventually showed multiple bleeding sites arising from the distal duodenum, proximal jejunum and colonic hepatic flexure. Deep push enteroscopy was performed on the same occasion, but only showed pooling of blood, with no source of active bleeding. Surgical opinion was sought but he was deemed unsuitable for any surgical intervention due to poor functional cardiac status.

In view of ongoing bleeding episode, he was started on high dose oral conjugated oestrogen 12.5 mg daily for 5 days after counselled on possible thrombotic risk with no further antiplatelet therapy. After the initiation of oestrogen, he had no more bleeding episode, and haemoglobin remained stable with no further blood transfusion requirement. He was discharged well with haemoglobin of 10.5 g/dL. Up to 150 days after initiation of oestrogen, no further bleeding episode or thrombotic event was noted.

DISCUSSION

Hormonal therapy was initially explored by Harrison in 1982 after observing few case series of epistasis improvement in patients with HHT during pregnancy and puerperium.[2] The mechanism of action of hormonal therapy is not well understood. Oestrogen and progesterone receptors have been detected in telangiectatic lesions in patients with hereditary haemorrhagic telangiectasia (HHT), and the hormone-receptor binding improved endothelial integrity in patients with HHT. In animal model, oestrogen was found to improve the vascular stasis within the mesenteric microcirculation and decreased mucosal blood flow. In patients on hemodialysis, oestrogens shorten bleeding time by the reduction of endothelial prostacyclin production.[3]

Hormonal therapy has been reported in several case reports and controlled/uncontrolled studies of gastrointestinal angiodysplasias or OGIB.[4-6] The results, however, were conflicting. In a study of 43 patients with OGIB who were treated with hormonal therapy, rebleeding was effectively stopped in 38 patients (follow-up of a mean time of 535 days).[7] However, two controlled studies on angiodysplasia bleeding did not demonstrate any benefit. Both studies had small number of sample and with lower dose of oestrogen used. This discrepancy suggest that dosing of oestrogen may play a role.[8,9]

Overall, the effectiveness of hormonal therapy remains unclear, except for the treatment of HHT, von Willebrand disease, chronic kidney failure and gastric antral vascular ectasia.[10] Its utilization in OGIB should be of last therapeutic resort. The treatment with oestrogen is not without risk, which includes thrombosis, gynecomastia, breast tenderness, fluid retention, heart failure, and vaginal bleeding in females.[7] In our patient, he had achieved hemostasis despite having multiple bleeding sites after 5 days of high dose conjugated oestrogen. Spontaneous resolution of the bleeding could be argued due to the cessation of antiplatelet. However, in this gentleman, he still experienced OGIB despite the antiplatelet therapy being stopped for more than 9 days.

CONCLUSION

Despite lack of convincing clinical data, we believe that hormonal therapy especially oestrogen at higher dose, remains one of the pharmacological therapy options in patient with difficult to manage OGIB.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

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Major Depressive Disorder in a Patient with Systemic Lupus Erythematous, Pulmonary Hypertension, and Hypercoagulation: A Case Report

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ABSTRACT

Major depressive disorder is characterized by the presence of single or repeated major depressive episodes, which are considered periods of 2 weeks of depressive moods featuring impaired neurovegetative functioning, psychomotor activity, and cognition, as well as suicidal thoughts. Major depressive disorder is commonly associated with other medical conditions, especially chronic and systemic medical illnesses. Cardiovascular diseases are among the most related, especially pulmonary hypertension, a cardiovascular disorder that results in increased pulmonary circulation pressure—with an average resting pulmonary arterial pressure of at least 25 mmHg—and which the WHO has associated with several other conditions, including connective tissue diseases such as scleroderma and systemic lupus erythematosus (SLE). The patient in this case is a 39-year-old woman diagnosed with major depressive disorder and SLE-associated pulmonary artery hypertension, which has been associated with hypercoagulable states, as observed in this instance. The complicated associations between these problems require collaboration between disciplines to establish optimal treatment integrity, with palliative care necessary to improve this patient's quality of life.

Keywords: *Depressive disorder, Pulmonary Hypertension (PH), Systemic Lupus Erythematous (SLE), Hypercoagulation.*

INTRODUCTION

Major depressive disorder is characterized by the presence of single or repeated major depressive episodes[1] and is usually associated with other medical conditions, especially chronic and systemic conditions. The overlapping clinical conditions of physical comorbidities, the neurovegetative symptoms associated with major depressive disorder, and the emotional response to physical illness complicate accurate diagnosis and provision of appropriate treatment for depression in a person with a medical illness.[2,3] Major depressive disorder is frequently observed to be a chronic condition, occurs two to three times more often among women than men, and features a prevalence of approximately 2–4% in the community. Prevalence increases by 5–10% among outpatients in primary care and by 10–14% among medical inpatients. These statistics indicate an association between physical illness and major depressive disorder.

Psychological disorders, such as depression

and anxiety, are often observed in patients with cardiovascular diseases.[4,5] Such psychological factors have also been implicated in increases in hospitalization and mortality rates among patients with cardiovascular disease, as well as decreases in their quality of life. A study comparing patients with heart disease who were not depressed with those who were depressed indicated that the latter group was more likely to be admitted as patients within the next 3 months. Additionally, the latter group was almost 50% more likely to die during the following year (29% compared to 20%).[4]

Heart failure is especially associated with decreased quality of life, describing the final stage of various cardiovascular diseases, including pulmonary hypertension (PH), which commonly causes right heart failure and has been defined as an increase in pulmonary circulation pressure, quantified as a mean resting pulmonary artery pressure of at least 25 mmHg.[6] The WHO has classified PH into five main groups: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to pulmonary disease or chronic hypoxia, PH due to chronic thromboembolic disease, and a miscellaneous group.[7–9] Women are more likely to experience PAH, with data indicating 65–80% predominance in their favor.

The first WHO classification group, PAH, can be idiopathic (Idiopathic Pulmonary Arterial Hypertension, IPAH), inherited (Heritable Pulmonary Arterial Hypertension, HPAH), related to drugs or toxins (Drug and Toxin Pulmonary Arterial Hypertension, DTPAH), or associated with other conditions (Associated Pulmonary Arterial Hypertension, APAH), such as connective tissue diseases including scleroderma and systemic lupus erythematosus (SLE). The prevalence of PAH among those with SLE has been estimated as 0.5–17.5%.[10] An autoimmune disease with varying clinical features, SLE can manifest as one of several autoantibodies or as the formation and deposition of immune complexes, among other immune processes. These complex clinical features and pathogenesis make SLE difficult to diagnose quickly.[11]

Notably, medical comorbidities may slow the remission of major depressive disorder, meaning a prompt diagnosis leading to multidisciplinary and collaborative treatment is needed to improve patient quality of life.

CASE ILLUSTRATION

A 39-year-old female patient presented to the emergency department complaining of shortness of breath since a week before the visit. The tightness was induced by activity, and the patient felt better in a sitting position. The patient also complained of a cough, a fever, and edema in both arms and legs. Urine volume had decreased since the previous month. Although the patient was initially suspected of having contracted COVID-19, two PCR swab examinations returned negative results. The patient had routinely visited the Cardiology Division, where she had been diagnosed with hypertension and given medication therapy in the form of digoxin, candesartan, beraprost, rivaroxaban, and furosemide. Additionally, the patient was in a hypercoagulable state and was routinely visiting the hematology and oncology clinic, where she received heparin as medication. The patient had no history of other chronic diseases.

The patient had been divorced from her husband 10 years earlier and had a 16-year-old daughter. The patient was living with her parents, daughter, brother, sister, brother-in-law, and nephew and was no longer working following 10 years of employment at a travel agency. She had decided to stop working to focus on caring for her child, feeling that she had grown distant from her daughter, who she reported as tending to ignore her, never wanting to talk or communicate with her. This led the patient to feel neglected. The patient felt that her daughter was much closer to her younger siblings and parents, which had made the patient feel very sad for many years. The patient had tried to talk to her daughter, but the child was unresponsive. Attempts to communicate this to her family left the patient feeling rejected. Additionally, the patient had no friends to talk to, feeling that, for more than 5 years, she had been sad, helpless, useless, and listless. Still, she had been able to move forward and did not have suicidal thoughts.

The consciousness of the patient on arrival was compos mentis. Her blood pressure was

97/77 mmHg, her heart rate was 81 BPM, her respiratory rate was recorded as 30 times per minute, her body temperature was 36.5° C, and her O_2 saturation was 98% with 10 liters of oxygen per minute (via simple mask). The patient could be categorized as having grade II obesity (BMI: 42.98 kg/m^2). A physical examination revealed marked pallor of the skin and conjunctiva and pitting edema at both lower extremities. There were wounds in the buttocks and breast folds. Physical examinations of the heart, lungs, abdomen, and other areas were not remarkable.

As mentioned, the patient's mental status was recorded as compos mentis (E4V5M6), and her appearance was described as that of an obese woman lying down with short breath and requiring assistance with self-care functions. She was in a calm psychomotor state and cried when telling the story of her daughter. The patient was cooperative. She could speak and answer spontaneously, fluently, and clearly. The patient was in a hypothimic mood with limited affect and presented coherent thoughts with a sense of helplessness, worthlessness, and preoccupation with her daughter. Her perception was good.

Laboratory investigations showed microcytic hypochromic anemia (Hb 7 g/dL), leukocytosis, neutrophilia, hyponatremia (128), hypokalemia (3.3), hypochlorite (95.8), hypocalcemia (1.0), normal T4, increased TSH, normal cortisol levels, increased bilirubin (total: 7.91, director: 5.56, indirect: 2.35), hypoalbuminemia (2.65), hyperglobulinemia (4.65), increased LDH levels (253), and increased D-Dimer (7730). The antinuclear antibody (ANA) profile examination results were positive, showing decreased C3 (78). Radiological findings showed cardiomegaly with minimal right-sided perihilar, paracardial infiltrates, and right side superior mediastinal enlargement. Meanwhile, CT angiography revealed dilatation of the pulmonary arteries, dilatation of the right atrium and right ventricle, and bilateral pleural effusions, features consistent with PH. Echocardiography showed normal left ventricular systolic (ejection fraction of 58.1%) and diastolic functions with diminished right ventricle systolic function (TAPSE: 9.8). The tricuspid valve was severely regurgitated, and transesophageal echocardiography showed atrial septal aneurysm with PFO and right heart dilatation, most likely indicating PH. Cardiology catheterization indicated IPAH.

The medical problems present in the patient's comprehensive multiaxial diagnosis were (i) axis I: dysthymia; (ii) axis II: histrionic personality; (iii) axis III: PH, SLE, hypercoagulation, anemia, pneumonia, subclinical hypothyroidism, obesity, obstructive jaundice; (iv) axis IV: underlying medical conditions, poor child and family relationships; and (v) axis V: a Global Assessment of 40 points for functional score. Psychosocial problems were bad relationships with family members, a sense of worthlessness, and preoccupation with past mistakes.

Pharmacological therapy and supportive psychotherapy validating empathy, along with psychoeducation and cognitive behavioral therapy (CBT) were planned for this patient. Medical therapy was also prescribed based on the patient's acute conditions of shortness of breath, dysthymia, poor perfusion, hypercoagulation, edema, and electrolyte disturbances. The patient was hospitalized at intensive care for circulatory failure, electrolytes, administration of anticoagulation to prevent thrombus formation and embolism, and administration of pharmacological therapy to treat the cause. The patient was to receive endothelin receptor antagonist drugs (namely, ambrisentan, bosentan, and macitentan).

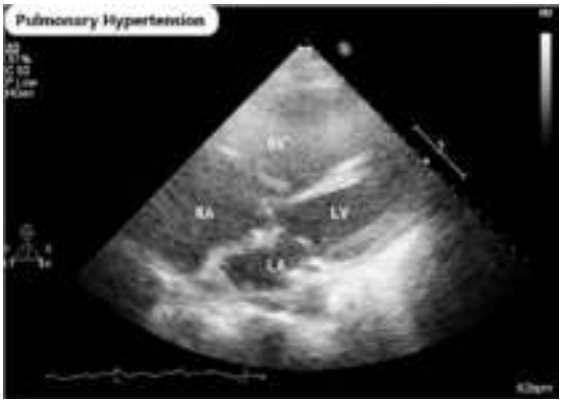

Figure 1.

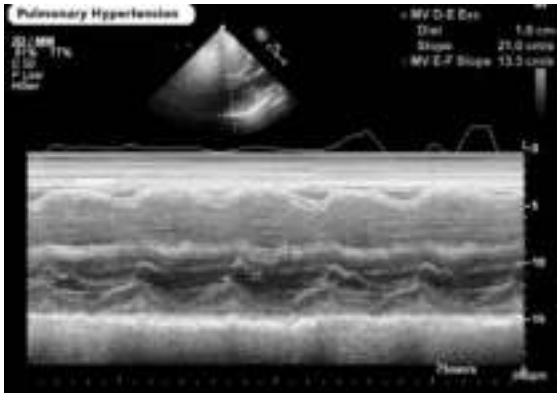

Figure 2.

DISCUSSION

Major depressive disorder is characterized by the presence of single or repeated major depressive episodes, which are considered periods of 2 weeks of depressive moods featuring impaired neurovegetative functioning (e.g., appetite, weight loss, sleep disturbances), psychomotor activity (e.g., loss of energy and interest, agitation, or retardation), and cognition (feelings of worthlessness, hopelessness, and guilt), as well as anxiety and suicidal thoughts.[1]

In this case, the patient was examined for mental status. Symptoms matched the criteria for major depressive disorder. The patient had experienced depressive moods for periods of 2 weeks for more than five years. Neurovegetative dysfunction was found in the form of decreased appetite and changes in sleeping patterns. Psychomotor activity disorders included loss of energy and interest. Additionally, impaired cognitive functioning was observed in the form of feeling worthless[1,12,13] to her family. The patient had divorced her husband 10 years earlier, almost certainly one of the stressors for the patient. Additionally, the patient's daughter was a teenager, and the patient and her daughter were living with her parents, daughter, brother, sister, brother-in-law, and nephew. The patient was no longer working, having worked for 10 years at a travel agency before deciding to stop working to focus on caring for her child. According to the patient, she had recently become less close to her daughter. All of these factors had acted as stressors for the patient, leading to poor decisions. Additionally, because she was not working and all her daily needs were paid for by her parents, her sense of worthlessness increased.

Major depressive disorder is usually associated with other medical illnesses, especially chronic and systemic medical conditions. The overlapping physical and neurovegetative symptoms of major depressive disorder and the initial normative emotional response to physical illness increase the challenge of making an accurate diagnosis. These factors also affect decisions on the appropriate treatment for major depressive disorder in a person with a medical illness.[2] Comorbidities challenge therapeutic approaches, increasing hospitalization and mortality rates, as well as decreasing quality of life.[14]

One of the medical diseases identified in this patient was PH, which, increases pulmonary circulation pressure.[4] Specifically, the patient was observed to have PAH, which is characterized by molecular and pathological changes in pulmonary circulation that primarily result in progressive vascular remodeling of the pulmonary arteries, increased pulmonary vascular resistance, and, ultimately, right heart failure and death. These changes are caused by several inflammatory, metabolic, and cellular changes that eventually promote occlusive lesions, in-situ thrombosis, and plexiform lesions. There is pro-thrombotic pathobiological evidence indicating an increased hypercoagulable state in PAH patients.[15]

In diagnosing PAH, findings from medical history, physical examination, radiographs, and electrocardiography (ECG) may reveal PH and right ventricular dysfunction. Physical examination of PH may reveal a systolic ejection murmur. Meanwhile, right ventricular failure causes systemic venous congestion, with signs including a high-pitched systolic murmur due to tricuspid regurgitation, as well as hepatomegaly, ascites, and peripheral edema. Echocardiography with Doppler can be used to initially screen to estimate pulmonary artery pressure and assess ventricular function. Right-sided cardiac catheterization is recommended as a confirmatory test for PH and can also be useful for assessing the reversibility of PAH using vasodilation therapy. Meanwhile, PAH patients should be screened clinically for possible nocturnal desaturation and obstructive sleep apnea. The complete blood

count, biochemical markers, prothrombin time, and activated partial thromboplastin time should all be checked as soon as possible, and an arterial blood gas analysis should be performed to rule out hypoxemia.[10,16]

Collagen-vascular disease screening can be performed by measuring the ANA, rheumatoid factor, and antineutrophil cytoplasmic antibody levels. Liver function tests, albumin, international normalized ratio, and platelet count may indicate either or both possible liver disease and portal hypertension. Brain natriuretic peptide (BNP from NT-proBNP) should be performed on patients as indicated. For patients at risk of HPAH, screening for gene mutations such as BMPR2 may also be considered. Ferum examination can also indicate patients at risk of PAH, with studies having found a prevalence of iron deficiency among patients with PAH. Meanwhile, histopathological lesions for patients with PAH are plexiform lesions, comprising medial hypertrophy, eccentric or concentric laminar intimal proliferation and fibrosis, fibrinoid degeneration, and thrombotic lesions.

In this case, the patient's medical history indicated severe symptoms in the form of shortness of breath and swelling, with TEE and cardiac catheterization confirming the presence of PH, good left heart systolic and diastolic functions (ejection fraction of 58%), and diminished right ventricular systolic function with tricuspid valve regurgitation. The laboratory test found an increased dimer value, prompting the diagnosis of a hypercoagulable state. That shortness of breath did not improve rapidly through acute management suggests the possibility of micro embolism associated with hypercoagulation.

Hypercoagulation is common in PH cases, with studies showing that PAH patients have increased plasma fibrinopeptide A and D-dimer levels, increased fibrinogen levels, and decreased fibrinolytic responses, especially in patients with IPAH. Fibrinopeptide A is produced when thrombin cleaves fibrinogen, indicating increased plasma thrombin activity. The procoagulant activity and fibrinolytic function of the pulmonary artery endothelium are also altered. This dysfunction is demonstrated by elevated levels of von Willebrand factor and plasminogen activator inhibitor type-1 in the plasma of PAH patients. Additionally, the pressure of blood flow to the vessel wall produces a thrombogenic surface, resulting in thrombotic lesions. In-situ thrombosis can be caused by abnormalities in some or all of the coagulation cascade, endothelial cells, and platelets. Tissue factor expression may be a major contributor to in-situ thrombosis formation, with tissue factor binding to factor VII to catalyze the activation of factor X, promoting thrombin formation and fibrin clot formation. Tissue factor expression is sensitive to changes in blood flow, hypoxia, growth factors—such as platelet-derived growth factors—and chemokines. Thromboxane A2, which stimulates activation of new platelets and increases platelet aggregation, increases in PAH patients, corresponding to a decrease in prostacyclin metabolites. Increased platelet production, activation, and aggregation can initiate a vicious cycle contributing to thrombosis.[15]

An assessment of the possibility of autoimmune disease was also performed for this patient, which is appropriate because group 1 PH can be associated with autoimmune disorders or connective tissue. The ANA profile results were positive, and the patient was diagnosed with SLE. Although the patient's symptoms did not show the abnormal clinical presentation related to SLE, autoimmune diseases with a broad clinical spectrum are known to impact specific target organs or systems. Autoimmune diseases also significantly undermine patients' quality of life.[17,18] Accordingly, this patient was classified as having WHO Group 1 PH related to autoimmune disease, commonly known as APAH.[10,11]

The causes of major depressive disorder are multifactorial, including biological, genetic, environmental, and psychosocial factors. Major depressive disorder was previously thought to be primarily due to abnormalities in neurotransmitters, particularly serotonin, norepinephrine, and dopamine. Although the real correlation of major depressive disorder with cardiovascular disease in terms of physio pathological mechanisms of depression is not fully known, some similarities have been found, including high levels of catecholamines,

cortisol, and inflammatory cytokines (IL-6, IL-1β, TNF-α), which also substantially impact the clinical and prognostic significance of depression. These conditions can increase hospitalization and mortality rates. Meanwhile, anxiety can negatively affect breathing quality and cause panic attacks and chest pain, ultimately worsening symptoms. Anxiety can also correlate with the dysfunction of the hypothalamic-pituitary-adrenal axis, which is commonly observed in cardiovascular disease.[19] Major depressive disorder negatively impacts patient quality of life and functional status, decreases physical activity levels, and worsens survival rates.[20] In this case, the patient exhibited symptoms such as helplessness, decreased appetite, and hopelessness, which were absolutely closely related to her cardiovascular disease, with the condition exacerbated by her patient's social conditions, particularly her relationship with her family.

In this case, the patient required proper treatment in the form of continued palliation. Palliative care is an interdisciplinary service and a comprehensive approach to care, with the purpose of improving quality of life and alleviating pain for patients with severe disease, regardless of prognosis. Core aspects of palliative care interventions include expert assessment of pain and other physical symptoms, psychosocial care, identification of treatment goals, and support for complex care and decision making. The optimal time to integrate primary or patient-specific palliative care varies according to the patient's needs rather than the prognosis. Additionally, palliative therapy focuses on how a clinician should assess and reduce emotional stress in a patient and their family.[21] Families should be invited to discuss and collaborate to create a positive atmosphere for improving the patient's quality of life.

Pain management and making a long-term treatment plan is also required. In this case, pharmacotherapy, in the form of serotonin selective reuptake inhibitors (SSRI) class drugs, was provided in combination with CBT therapy. A few days after the follow-up visit, the patient began to accept her condition and build relationships with her daughter and family. The combination of pharmacotherapy and psychotherapy is more effective than independent treatment for depressed patients with cardiovascular disease. The first choice of SSRIs followed convention, with SSRIs usually administered with consideration of the effectiveness and tolerability of the class as a whole. Nonetheless, other classes and atypical antidepressants have also shown treatment efficacy.

The choice and type of psychotherapy can be selected according to patient needs, with CBT and interpersonal therapy most commonly used to treat major depressive disorder.[1] A structured therapy based on a cognitive-behavioral model, CBT is based on the notion that cognition affects emotions, which in turn influence behavior. This process can modify thought cycles, emotions, and behaviors that worsen moods, with CBT treatment interventions focusing on modifying cognition and behavior to improve mood. The cognitive aspects of CBT can identify and challenge negatively biased thoughts that promote major depressive episodes, with CBT involving providing evidence to support and refute this thinking and reshaping perspectives to demonstrate that a problem is not so big or complex. Furthermore, CBT techniques seek to reinforce healthy or prosocial behavior. In patients with a medical illness, this may include a focus on scheduling, problem-solving, and prioritization, which can help patients develop a sense of reasonable control over their lives.

Pharmacological management for the patient's PH was also provided. Treatment options vary. For example, diuretics are often useful for PAH patients with signs of congestion on the right side of the heart, as evidenced by lower limb edema, ascites, liver congestion, or raised jugular veins. Digoxin is mainly used to treat PAH patients with atrial tachyarrhythmias and require inotropic properties. Meanwhile, endothelin receptor antagonists (i.e., ambrisentan, bosentan, and macitentan) activate the endothelin system, causing an increase in endothelin-1 vasoconstrictor levels among PAH patients. That is, the drugs act as antagonists in this pathway. Meanwhile, regarding phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil) and guanylate cyclase stimulators (riociguat), cyclic

guanosine monophosphate (cGMP) causes vasodilation via the nitric oxide/cGMP pathway, with PDE-5 decreasing cGMP and PDE-5 inhibitors prevent such degradation. Regarding prostacyclin analogs (beraprost, epoprostenol, iloprost, treprostinil) and prostacyclin receptor agonists (selexipag), prostacyclins are potent vasodilators, with dysregulation of prostacyclin synthesis metabolism having been identified in PAH patients.

Finally, the patient received anticoagulation therapy to treat hypercoagulation. According to the guidelines of the European Society of Cardiology and the European Respiratory Society 2015, anticoagulation is a class IIb recommendation, indicating that its usefulness and efficacy are not optimal but that it can be considered. Several retrospective and observational studies have demonstrated benefits for patients who have been anticoagulated using warfarin. However, research and data remain limited and divergent, likely due to the heterogeneity of PAH patients. Notably, the clinical use of anticoagulation to treat PAH patients varies widely.

A thorough assessment of patients experiencing mental health symptoms should not rule out medical or biological causes of the symptoms. Treatment of these patients involves an interdisciplinary approach, with both specific medications and multidisciplinary consultations required for patient treatment. The patient's hypercoagulable state, in association with PH, was also of concern, possibly creating micro embolism and making clinical improvement difficult to achieve. Additionally, while psychiatrists and therapists provide therapy to ensure open and direct lines of communication and enable patients to receive the best care,[19] it is also important to focus on the role of the patient's family, particularly, in this case, her child, siblings, and parents. Depression with medical comorbidities is not currently considered a distinct diagnostic entity; instead, it forms part of a symptom of an ongoing depressive disorder. Nonetheless, medical conditions can be a risk factor for depression, constituting stressors that can trigger or exacerbate depression among patients with other tendencies (and vice versa).

CONCLUSION

Major depressive disorder is characterized by 2-week periods of depressive moods featuring neurovegetative dysfunction—in the form of a decreased appetite and changes in sleeping patterns—and impaired psychomotor activity—including absences of energy and interest. Additionally, impaired cognitive functioning is observed, generally as feelings of helplessness and worthlessness. In this case, the patient was also observed to be suffering from APAH, a version of PH associated with an autoimmune disease. Pulmonary hypertension has also been closely related to hypercoagulation. Importantly, as observed in this case, psychosocial problems can clinically aggravate patients with cardiovascular disease, producing a complex relationship between the diagnoses that requires collaborative care between disciplines to establish optimal treatment integrity. Ultimately, in cases such as the one this paper has discussed, palliative care is required to improve a patient's quality of life.

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Aquaretics Use in Acute Decompensated Heart Failure (ADHF) Patients: A Literature Review

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ABSTRACT

This is a literature review of the use of aquaretic in patients with acute decompensated heart failure (ADHF), including the physiologic function of vasopressin and its mechanism of action in heart failure patients, and aquaretic drugs with their respective risks and benefits.

Vasopressin is one of several hormones that can cause hyponatremia and worsen congestion in ADHF patients. Aquaretics are a class of drugs that have an antagonistic effect on vasopressin receptors, especially V2R. Aquaretics use in ADHF patients can provide relief for congestive symptoms with no serious adverse effects. In-depth additional understanding regarding aquaretics may be useful for clinical judgments in treating ADHF patients.

Keywords*: acute decompensated heart failure (ADHF), aquaretics.*

INTRODUCTION

Heart failure is a global pandemic, with a rapidly increasing prevalence, affecting at least 26 million people worldwide.[1] In the United States of America, the *American Heart Association* (AHA) estimated that, between 2013 and 2016, around 6.2 million people suffered from heart failure. This number is projected to increase in 2030, with an increased prevalence rate of 46% from the available data in 2012, more than 8 million patients will have heart failure. This burden of disease will increase from 30.7 billion US dollars in 2012 to 69.8 billion US dollars in 2030.[2]

Generally, acute heart failure (AHF) is defined as a rapid onset or worsening of heart failure signs and symptoms that need urgent medical treatment. AHF may present as a first occurrence (*de novo)*, or more frequently, due to acute decompensation of chronic heart failure, commonly known as acute decompensated heart failure (ADHF).[3] More than 1 million hospitalizations per year in the United States is due to ADHF; thus, this condition is the main reason for hospitalization in patients aged 65 or more.[4] ADHF causes a heavy financial burden on the healthcare system, most of which are closely related to hospitalization. The in-hospital mortality rate of ADHF is around 4-7%; the 3-month post-discharge mortality rate is around 7-11%, and the 1-year post-discharge mortality rate is 36%. According to studies in the United States, the length of hospitalization is around four days, and in Europe, it can be around 6-11 days. Despite this long-standing burden, only a few steps were achieved within the last couple of years in medical treatment for ADHF.[5]

The management of ADHF was written by the European Society of Cardiology (ESC) in

2016 and the American College of Cardiology Foundation (ACCF) in conjunction with the AHA in 2013. However, aquaretic (vasopressin receptor antagonist) use was only considered in patients with volume overload and severe resistant hyponatremia.[3,6]

One of the pathophysiologies in heart failure patients is an increased level of vasopressin. Through the activation of the V1 pathway, there is an increase in peripheral resistance and pulmonary capillary wedge pressure (PCWP), whereas stroke volume and cardiac output decrease.[7] Vasopressin receptor antagonist drugs bind three receptors, V1R that affects vasoconstriction, V2R that has a role in water reabsorption, and V3R that affects the adrenocorticotropic hormone.[8] This literature review highlights the mechanism, benefits, risks, and use of aquaretics in ADHF patients.

PHYSIOLOGY OF VASOPRESSIN

Vasopressin, or antidiuretic hormone (ADH), is a hormone secreted in the hypothalamus and stored in the posterior pituitary. This hormone has several roles in controlling the body's osmotic balance, blood pressure regulation, sodium homeostasis, and kidney function.[9] These V receptors can be classified into V1 vascular (V1R), V2 renal (V2R), V3 pituitary (V3R), dan oxytocin (OTR) subtypes.[10]

V1R receptors are found in vascular smooth muscles and result in vasoconstriction by increasing the intracellular calcium levels. V1R receptors are also found in the brain, testes, liver, and renal medulla; however, the function is still unknown. Platelets are known to express V1R receptors, which facilitate thrombosis; however, there is varying platelet aggregation response in different individuals.[11]

V2R receptors are G-protein-coupled receptors (GPCR) found in the basolateral plasma membrane in the collecting duct. Vasopressin bound to this receptor will increase water absorption by regulating aquaporin-2 (AQP-2).[12] AQP-2 plays a crucial role in regulating short- and long-term water permeability in the collecting duct. Short-term regulation results in increased water permeability 5 to 30 minutes after vasopressin concentration increases, while the long-term regulation happens when vasopressin level increases within days, causing increased AQP2 levels in cells.[13] V3R correlates with the secretion of ACTH by binding the receptors in the anterior pituitary.[14] **Table 1** describes the vasopressin receptor's physiological effects.

VASOPRESSIN IN HEART FAILURE

Vasopressin levels will increase in heart failure patients as the functional severity of the disease increases.[15] The increase in vasopressin is modulated by three mechanisms: the osmoreceptor, the baroreceptor, and the renin-angiotensin-aldosterone system (RAS). Vasopressin production is primarily regulated by the osmoreceptors in the hypothalamus; a 1-2% decrease in plasma osmolality will suppress vasopressin level so that maximal aquaresis is achieved. Heart failure patients have a decreased cardiac output that causes lower arterial filling, leading to baroreceptor activation in the carotid sinus, aortic arch, and left ventricle. This pathway has a lower sensitivity in regulating vasopressin but is much more potent in heart failure patients. On the other hand, the RAS system regulates the vasopressin by direct secretion of the hormone angiotensin II.[16]

The increase in vasopressin leads to lower excretion of water and, thus, causes

Table 1. Physiologic Function of Vasopressin Receptor.[11–14]

Vasopressin Receptor	Location	Physiologic Function
V1R	Vascular smooth muscle (mainly), thrombocyte, brain, testicles, liver, cardiomyocyte, and kidney medulla	Vasoconstriction (mainly), gluconeogenesis, and thrombocyte aggregation
V2R	Collecting duct of the kidney	Increasing water reabsorption through AQP2
V3R	Anterior pituitary gland	Secreting ACTH

hyponatremia. Water retention will exacerbate congestion in heart failure patients, while hyponatremia independently correlates with increased mortality. Chronically, this process will cause heart remodeling.[17] (**Figure 1**)

PHARMACOLOGY OF AQUARETICS

Aquaretics are a class of drugs that induces water excretion without electrolyte excretion. This group of drugs refers to vasopressin receptor antagonists, especially V2 receptor antagonist.[19] Peptide vasopressin receptor antagonists have been developed since 1960; however, their efficacy is low. Peptide antagonists lose their antagonistic effects and become agonists when administered chronically and can only be given parenterally. Vaptan is a non-peptide vasopressin receptor antagonist that is orally active.[20] **Table 2** shows the available aquaretics.

Conivaptan is a type of vaptan with affinity to V1 and V2 receptors, with dose-dependent effects. Conivaptan is approved by the Food and Drug Administration (FDA) for its hyponatremia usage with an intravenous dose of 40-80 mg/day. However, this is not recommended for heart failure patients because no significant difference in the effect found when applied in the patients compared to placebo.[21]

Lixivaptan is an orally active vasopressin receptor antagonist with non-peptide and V2 receptor-selective (100:1 with V1) characteristics. Similar to Conivaptan, the potency of aquaresis in Lixivaptan is also dose-dependent.[22] Currently, this drug is undergoing phase 3 clinical trials in patients with autosomal dominant polycystic kidney disease (ADPKD).[23]

Mozavaptan (OPC-21268) is a selective V2 receptor antagonist (10:1 with V1), which can be given parenterally. The aquaretic effect from mozavaptan is dose-dependent (0,017-1 mg/kg) and still has its effect after two hours. When administered in high doses (0,75-1 mg/kg), its aquaretic effect has the same potency as 20 mg furosemide.[21] Mozavaptan is only used in Japan, and its clinical indication is for the inappropriate secretion of antidiuretic hormone in paraneoplastic syndrome.[20]

Satavaptan is an orally active and highly selective V2 receptor antagonist (112:1 with V1).[24] Satavaptan has a long half-life and can be

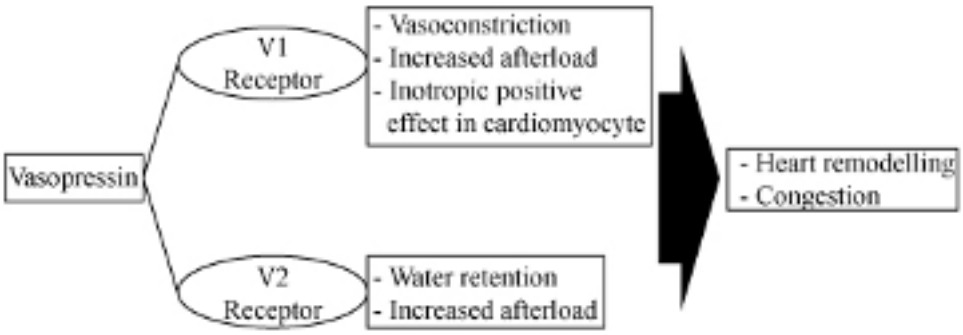

Figure 1. Role of vasopressin in heart failure.

Table 2. Aquaretics type available.[20]

Receptor Antagonist Type	Examples
V1/V2	Conivaptan
V2	Lixivaptan
	Mozavaptan
	Satavaptan
	Tolvaptan

given once daily with a 5-50 mg/day dose. This drug is metabolized in the liver and eliminated with the feces.[20]

Tolvaptan is a type of aquaretic with high selectivity to the V2 receptor (29:1 with V1) and has no biologic activity with V3. Around 40% of oral Tolvaptan dose will be reabsorbed, with maximal concentration achieved in 2-4 hours (not affected by foods). Dosing of tolvaptan starts from 15 mg once daily, and may only be increased after 24 hours until a maximum dose of 60 mg/day.[25] Tolvaptan is one of the few drugs accepted by the FDA for the treatment in hyponatremia in SIADH, heart failure, and liver failure patients because of its safety and efficacy. On the contrary, other vaptans are still under clinical trials or have already been rejected because of its safety and efficacy.[26]

BENEFITS AND USES

Decompensation in ADHF patients occurs due to increased sympathetic nervous system activation, ADH, and renin-angiotensin-aldosterone (RAAS). These neurohormonal activations cause upregulation in the RAAS and intrarenal vasoconstriction, thus increasing sodium and water retention. Diuretics such as furosemide, metolazone, and spironolactone have become one of the mainstay therapies for ADHF patients. Aquaretics are added to increase fluid and osmotic balance by inhibiting water retention without affecting the electrolytes in ADHF patients.[27]

Efficacy

Most patients hospitalized for ADHF are complaining about their symptoms due to volume overload (congestion). Decongestion through diuresis is one of the primary treatment in these patients, and some parameters such as weight loss, and urine output could be attributed as objective parameters to assess the efficacy. ACTIV trial, a randomized clinical trial (RCT) done by Gheorghiade *et al.* compared three doses of tolvaptan (30 mg, 60 mg, and 90 mg) with placebo. Patients aged 18 years and older with decompensated heart failure with stable hemodynamic were included. Tolvaptan was useful in weight loss on day one and significantly provided relief for congestive symptoms. An increase in sodium level was found in patients with a Tolvaptan regimen, while a small decrease was found in patients with a placebo regimen. Tolvaptan used in adjunction to standard therapies such as potassium-sparing diuretics will allow greater diuresis independent of the dose.[28]

This greater diuresis effect is reflected by one of the symptoms which is dyspnea. A meta-analysis from Luo et al, stated add-on tolvaptan was shown to be more effective in relieving short-term dyspnea than traditional diuretics alone (RR = 1.12 [1.05-1.18]). In addition to relieving dyspnea, tolvaptan as an add-on therapy was also more effective at reducing edema and body weight, as well as urine output (RR = 1.08 [1.02-1.15], MD = -0.82 [-0.94 – 0.71], MD = 0.49 [0.39 – 9.60] respectively).[29] This finding is similar with meta-analysis from Ma, et al, which included 7 RCT with 937 patients showed that Tolvaptan as an adjuvant therapy may reduce body weight and increase sodium levels in ADHF patients significantly.[30]

In contrast, TACTICS-HF by Felker, et al showed that, despite of greater weight loss and net fluid loss in the tolvaptan arm compared in placebo, but dyspnea relief by Likert scale was similar between these 2 arms at 8 hour and 24 hour (p: 0.59, and 0.80 respectively). These 2 arms were received standardized loop diuretic which consist of IV furosemide equivalent to their total daily oral outpatient dose (low dose arm in DOSE study). These findings may represent that despite net fluid loss is higher, time is needed for distribution of fluid out of the extravascular spaces into the circulation. Median length of stay was similar in both groups (5 days), and other clinical endpoints such as post-discharge outcome in 30 days was similar.[31] Konstam, et al has similar finding in his RCT, which tolvaptan has rapid and persistent weight loss, but not associated with improvement in dyspnea at first 8 – 24 hours (assessed with Likert dyspnea scores), but at day 3 dyspnea reduction was greater and significant in tolvaptan arm.[32] These findings suggest that further research is needed to develop more strategies for decongestion in patients with ADHF.

Loop diuretic is the mainstay therapy for congestion in patients with ADHF and tolvaptan add-on has shown great efficacy to relieve the congestion, but tolvaptan has been studied as monotherapy in patient with ADHF. AQUA-AHF, a randomized pilot study conducted by Ng et al, evaluating tolvaptan as monotherapy (30 mg oral, daily) in patients with HF that required hospitalization for decongestive therapy with hyponatremia compared to loop diuretics (5mg/h IV). This study showed that urine output, and net fluid balance were better in the furosemide group, but did not have significant differences in median between groups. Renal function is also better in the furosemide group, but not statistically significant. Oral tolvaptan monotherapy was associated with similar diuresis compared with IV furosemide, but not superior.[33] Larger studies are needed to further address this finding.

Diuretic resistance (DR) is a common challenge in treating ADHF patients. Patients with such condition are commonly treated with a combination of diuretic regiments. Current guidelines recommend adding a second diuretic such as thiazide, but it has limited data for the recommendation. Cox et al, conducted a trial to compare the combination of diuretic strategies, 5mg oral metolazone twice daily vs 500 mg IV chlorothiazide twice daily vs 30mg tolvaptan daily, concomitantly with high-dose IV furosemide. This study showed that, tolvaptan has similar results in term of weight loss with other diuretic, but only tolvaptan was associated with an improved urine output-based diuretic efficiency, and smaller decreases in serum sodium and chloride compared to others.[34]

Renal Properties

Patients that require more diuretic agents are linked to worsening renal function (WRF), this finding makes researchers conduct some study. Although the impact of renal function during ADHF is less defined, there have been some studies conducted to clear things up. A RCT conducted by Kimura et al, which compared addition of early tolvaptan administering (24 hours) to fixed furosemide dose (20mg/day) with furosemide that dosed up to 30mg/day, had significantly WRF and natrium serum level. A kaplan-meier analysis for survival free of cardiac death, or readmission for heart failure during the 90 days after discharge was done. Event free rate was significantly lower in the persistent WRF (p-WRF) subgroup, and the incidence of p-WRF was significantly lower in the tolvaptan group.[35]

This renoprotective benefit of tolvaptan as add-on therapy is also observed by Yamamoto et al, in their retrospective study. Changes in serum creatinine (Cr) was significantly increased in the non-tolvaptan group (+0.2 mg/dL vs -0.1 mg/dL), and the changes of GFR was significantly decreased in non-tolvaptan group (-2.7 mL/min/1.73m2 vs +1.4 mL/min/1.73m2). The WRF rate in the tolvaptan group was significantly lower (2.5% vs 15.4%) especially in the heart failure with preserved ejection fraction (HFpEF) patients. When multiple logistic regression performed for analyzing the predictors of WRF, tolvaptan also found to be an independent factor for reducing WRF (OR: 0.14 [0.02-0.98]).[36] These similar results also found by Kin et al, tolvaptan add-on therapy had lower incidence of WRF (8.5% vs 24%), and tolvaptan add-on therapy was an independent factor of preventing WRF.[37] But these results were varied, Felker et al in his study showed that WRF was more frequent in tolvaptan arm than in placebo arm (39% vs 27%).[31]

Wang C, et al showed in their meta-analysis that Tolvaptan decreased the rate of WRF compared with furosemide. Tolvaptan could also elevate the sodium level as fast as 2 days, indicating that tolvaptan was more suitable for ADHF with hyponatremia.[38]

Long-term Effect

Konstam *et al.* conducted a trial that included patients aged 18 years or older with reduced left ventricular ejection fraction, NYHA III/IV symptoms, and hospitalization caused by ADHF. The patients were randomized to receive a placebo or 30 mg/day Tolvaptan (standard therapy was given to both groups). In the short term, when added to standard therapy, Tolvaptan showed improved signs and symptoms of ADHF with no severe adverse reactions.[39] In the long term, Tolvaptan was non-inferior for mortality compared to standard therapy (Kaplan Meier analysis for mortality is 25% in the Tolvaptan group and 26% in the placebo group, and death

from cardiovascular causes or first hospitalization is 42% and 40.2%, respectively). [40] Wang C *et al.* also showed that tolvaptan was not inferior in mortality and prevented rehospitalization compared to conventional therapy, but a subgroup analysis showed that more than 15mg/day of Tolvaptan had the highest probability of achieving the best efficacy in preventing mortality and rehospitalization.[41]

However in Asian population, Nakao et al. in his meta-analysis showed that, compared to the conventional therapy Tolvaptan as add-on therapy did not show to improve long-term mortality and HF readmission in Japanese patients with HF. (OR: 1.02 [0.69 – 1.52], and OR: 0.73 [0.24 – 2.22] respectively). [42]

Cardiac remodeling prevention is one of the hypotheses that encourages the possible beneficial use of Tolvaptan. Udelson *et al.* conducted an RCT to examine the effects of Tolvaptan on changes in the left ventricular volume over time. There were no significant changes in the left ventricular end-diastolic volume (LVEDV) after one year of observation.[43] However, since this study was only conducted in stable HF patients, more studies are needed to confirm the cardiac remodeling effect of vaptans in patients after hospitalization due to ADHF.

Cost Effectiveness

Cost is one of the topics currently being considered and studied thoroughly. Dasta *et al.* conducted a study in 2018 that analyzed data from the Hyponatremia Registry (HNR), a multicenter and global observational study of management of hospitalized patients with euvolemic or hypovolemic hyponatremia. Seven hundred sixty-two patients, who were hospitalized because of heart failure, were analyzed. The data showed that patients administered with tolvaptan had a shorter hospitalization duration than patients with water restriction only (4 vs 6 days). Additionally, the average cost of 15 mg and 30 mg was compared with the average cost of hospitalization per day in the United States. Tolvaptan use was estimated to be 2295 USD cheaper than only water restriction regimen. However, the weakness of this study was only relying on data taken from HNR, which might present with input errors. Furthermore, the sample characteristics cannot be determined as in an experimental study. The cost of hospitalization is different in each country; therefore, this research cannot be used as an international reference.[44]

General Usage of Vaptans

Tolvaptan is used once daily orally with flexible titration. The starting dose is 15 mg/day and can be titrated to 30 mg/day after at least 24 hours and up to 60mg/day. During the initiation and titration, clinicians should frequently monitor the electrolytes and volume. Tolvaptan is contraindicated in patients with hypovolemic hyponatremia, anuria, hypersensitivity, concomitant use of potent CYP3A inhibitors, urgent need to raise serum sodium acutely, and inability to respond to thirst. Chronic use of tolvaptan can cause liver injury; thus, tolvaptan should not be given for more than 30 days to minimize the risks. Patients with cirrhosis should be monitored carefully as GI bleeding may occur.[45]

VRA use has been mentioned before in the 2013 ACCF/AHA guidelines for patients hospitalized with volume overload and severe hyponatremia and with a IIb class of recommendation and a B level of evidence.[6] On the other hand, the 2016 ESC guidelines also stated that VRA, such as Tolvaptan, can treat patients with volume overload and resistant hyponatremia, but did not state the class of recommendation nor the level of evidence.[3] These guidelines should be updated because newer evidence showed that FDA-approved vaptan such as Tolvaptan could be used as an adjuvant therapy to standard therapy (loop diuretic and/or MRA) to lower the use of more loop diuretics. This is important because higher doses of loop diuretics may worsen the renal function, and the addition of VRA provides better relief of congestive symptoms and stable serum sodium levels. VRA can still be used in patients with ADHF without hyponatremia, but ADHF patients with hyponatremia may get the most benefit.[30,35,41,46]

Risks

The use of vasopressin receptor antagonists can cause some side effects, such as thirst,

pollakiuria, and dry mouth. Thirst is found in 29% of patients and may become a problem if the patients increase their fluid intake.[44] In the administration of Conivaptan, 9.8% of patients experienced a rapid correction of serum sodium (>12 mEq/l/day) with no neurological symptom drawbacks especially the central pontine myelinolysis (CPM).[48]

Tolvaptan use is safe and only has some minor adverse reactions. An RCT found that 39.2% of patients complained of thirstiness, but these side effects were not prominent if the drugs were only given for 7-14 days. Other studies also reported that thirst was only felt mostly during the first three days.[49,50] Some case reports demonstrated that tolvaptan use in the elderly may cause liver damage.[51] The risk of liver damage in patients with ADPKD is well known. In an RCT of 961 patients, 1.5% of patients stopped the drug due to liver dysfunction, 4% of patients had a significant improvement in liver function, and 0.9% of patients had an increase in bilirubin.[52] However, no studies have reported liver damage in patients with AHF, especially ADHF.

A retrospective study by Fujioka et al found that although the continuous use of tolvaptan after discharge did not affect mid-term cardiac events of HF overall, it may be associated with increased cardiac events in the subgroup with preserved renal function. The exact cause was not determined, but the author argued that thirst, a side effect of Tolvaptan, might have increased water intake after discharge. This result suggested that the use of Tolvaptan might need to be limited to in-hospital management of ADHF.[53]

In laboratory animals, Conivaptan exerted fetopathic effects at doses that were less than the therapeutic dose. This delayed labor in rats at doses that were equivalent to their therapeutic doses. Thus, Conivaptan has been considered in Pregnancy Category C by the FDA. Another thing to consider is that the administration of Conivaptan can increase plasma concentrations of midazolam, simvastatin, digoxin, and amlodipine. Conivaptan is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), leading to serious drug-drug interactions. Tolvaptan has less potential for drug-drug interactions. Coadministration of Conivaptan with potent inhibitors of (CYP3A4), such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated. Due to this drawback, an oral preparation of Conivaptan has not been developed.[47]

There have been efforts to develop novel vasopressin antagonists, one of which is the highly V2 selective Lixivaptan. The BALANCE trial, an RCT designed to evaluate the effect of Lixivaptan in ADHF, reported a statistically significant but modest increase in sodium concentration. However, there was an unusually high number of deaths early in the Lixivaptan group for unclear reasons – 15 patients in the first ten days of treatment versus four in the placebo group. This raised concerns about the safety of Lixivaptan use in patients hospitalized with ADHF. Thus, on September 13, 2012, the FDA voted unanimously against recommending Lixivaptan for the treatment of hypervolemic hyponatremia.[54]

CONCLUSION

The use of aquaretics in patients with heart failure is well known in scientific writing, but this has only focused on the short-term, long-term, and the safety of their use. The use of aquaretics, especially tolvaptan, with a starting dose from 15 mg/day titrated up to 60mg/day may lead to good outcomes as adjuvant therapy in reducing symptoms from congestion such as shortness of breath, and objective parameters such as weight reduction, and in correcting hyponatremia. This use of the drug is non-inferior in terms of mortality compared to standard therapy. Clinicians need to investigate more on aquaretics to provide the best therapy for ADHF patients.

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Colonoscopy, Biomarkers, and Targeted Therapy in Colorectal Cancer

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ABSTRACT

This review highlights the most versatile diagnostic test of colonoscopy for CRC. It remains the gold standard diagnostic tools for CRC, and to prevent CRC by screening and removing the polyp or premalignant lesions. This work also provides the most promising biomarkers, which highlights the application of the novel biomarkers in conjunction with clinical and pathologic features have allowed for more individualized approaches and targeted therapy to patients with CRC.

CRC is the third most common cancer diagnosed, and the second leading cause of cancer-related deaths worldwide. With a population totaling 273,523,621 people, Indonesia has an estimated of 396,914 new cases of all cancers and 234,511 cancer-related deaths. Among those cancer cases, an estimated of 34,189 new CRC cases and 17,786 CRC deaths occurred in 2020. Most of CRC cases were located in the rectum compared to those in the distal colon or proximal colon. Clinical signs, symptoms and therapeutic approaches vary, depending on the stage and the location of CRC. Those cancer locations are different in terms of their associated molecular alterations.

Biomarker tests of tumor tissue from colonoscopy biopsy can help doctors to select a specific CRC treatment, and the tests can be used to determine prognostic value, predictive factors and the targeted therapy. Targeted therapies are recommended for advanced or mCRC patients with KRAS/NRAS/BRAF mutated or wild-type tumors, HER2-amplified tumors, and NTRK gene fusion-positive, while immunotherapy is only offered for tumor with MSI-High (dMMR) status. The biomarkers and targeting approaches against colorectal CSCs are being developed and will be quite challenging.

***Keywords**: Colonoscopy, colorectal cancer, biomarkers, cancer stem cells, targeted therapy.*

INTRODUCTION

There were an estimated 19.3 million new cases of all cancers and approximately 10 million cancer-related deaths worldwide in 2020. Colorectal cancer (CRC) is the third most common cancer, and the second leading cause of cancer deaths among all cancers worldwide, with an estimated of 1,931,590 new CRC cases (10% of all cancers), and 915,880 colorectal cancer deaths (9.2% of all cancer deaths) in 2020. With a population totaling 273,523,621 people, Indonesia has an estimated of 396,914 new cancer cases and 234,511 cancer-related deaths. Among those cancer cases an estimated of 34,189 new CRC cases (8.6% of all cancers), and 17,786 CRC deaths (7.6% of all cancer deaths) occurred in 2020. Other countries with increasing populations also experience similar phenomena.[1-3] Most of CRC cases were located in the rectum (74.6%) compared to those in

the distal colon (18.8%) or proximal colon (6.6%).[3,4] More than 50% of CRC patients will develop metastasis, and approximately 25% of them present with metastasis at initial diagnosis. Clinical signs and symptoms vary depending on the location and the stage of the tumor. Those locations are also different in terms of their associated molecular alterations.[3,4]

Colonoscopy and biopsy of the tumor tissue are important in CRC, and it has become a very popular method for primary CRC screening. It allows for early-stage cancer detection and polyps detection and removal. Sporadic CRCs may develop from adenomatous polyps and from sessile serrated lesions.[5,6]

Molecular testing of CRC from tumor tissues or biomarkers has important implications for the selection of treatment. The testing can also be used to determine prognostic value for molecular predictive factors and targeted therapy. Cancer locations, whether the tumor is at proximal colon, distal colon or rectum, are also different in terms of their associated molecular alterations and response with chemotherapy.[3,4,7-9]

CRC PREVENTION

Most polyps identified can be managed by conventional polypectomy, and they do not pose a significant challenge for resection to an adequately skilled and trained endoscopist.[10] The main endoscopic techniques that are available for removal of colon polyps, or early cancer and precancerous growths are as follows: a) Polypectomy, b) Endoscopic Mucosal Resection (EMR) and c) Endoscopic Submucosal Dissection (ESD).[10,11] Colonoscopy is a 1-step CRC screening test, and it is the most appropriate screening test and diagnosis of CRC.[5] With appropriate training, ESD is preferred over EMR as the first-line therapy for resection of colorectal polyps, without restricting to lesion greater than 20 mm and those with high suspicion of submucosal invasion.[11]

CLINICAL MANIFESTATION

Clinical signs and symptoms vary based on the location, the tumor size and the stage of CRC.[3,4] CRC may not cause symptoms in the early stages. If it does, the symptoms may include a change in bowel habits, such as diarrhea, constipation or a change in the consistency of the stool, and these symptoms can last for more than a few days. The change in bowel habits can also induce feeling that the bowel does not empty properly, or result in blood in the stool from the rectum (hematochezia) that is dark brown or bright red in colour, abdominal pain, cramping, bloating, feeling full, fatigue or tiredness, a decrease in appetite, unexplained iron deficiency anemia, and unexplained weight loss. CRC should be classified into several subgroups defined according to tumor location, rather than as a single entity, whether at proximal, distal colon or rectum. In clinical practice, different manifestations, molecular alterations and survivals have been observed in CRC patients with tumor originating from different sub-sites of the colorectum.[3,4,7,12-16]

Tumor location plays a critical role in predicting survival. Right colon cancer patients or proximal colon cancer had worse survival especially in the subgroups including stage III or IV disease.[3,4,12,14] Tumors in the proximal colon or right colon rarely cause symptoms of obstruction. Stool is relatively liquid as it passes through the ileocecal to the cecum and ascending colon. Tumor usually forms ulceration, chronic occult bleeding, microcytic hypochromic anemia due to iron deficiency, fatigue and weight loss. Stool has become more shaped as it passes through the transverse colon to the splenic flexure, descending colon and sigmoid colon (distal colon). Tumor in the distal colon can interfere with the passage of stool causing symptoms of abdominal pain or cramps, altered bowel habit, decreased stool caliber, or overflowed diarrhea. In addition, it sometimes causes symptoms of obstruction and perforation. Cancer located in the rectum will result in hematochezia, tenesmus, small-caliber stools due to narrowing of the rectum caused by the tumor. CRCs spread to other parts of the body by direct extension into adjacent structures and metastasis through the lymphatics and blood vessels. The favoured metastatic sites of CRC are lymph nodes, liver, lung, brain, bone, and peritoneum. Patient with metastatic CRC (mCRC) to the liver may have signs of right upper quadrant abdominal pain,

ascites, jaundice, or symptoms and signs from cancer spread to the lungs. Other symptoms include those from local invasion or perforation to bladder or vagina.[7,12-16]

DIAGNOSTIC EVALUATION

Physical Examination

Physical examination findings can be very nonspecific (e.g., fatigue, weight loss) or normal, early in the course of colon cancer. The examination is performed with specific attention to the abdominal mass, especially at the right and left iliac fossa, right upper abdomen, as well as to possible metastatic lesions, including enlarged lymph nodes, hepatomegaly, and others. Examination includes the use of digital rectal examination (DRE). Patients with proximal colon cancer, especially at the cecum may have abdominal mass, particularly at the right iliac fossa, while patients with sigmoid cancer will have palpable mass at the left iliac fossa. Common signs and symptoms of emergencies due to complications of CRC should be examined, such as peritonitis from perforation, or obstruction. Other signs, such as jaundice, hepatomegaly, ascites, may occur with liver metastasis.[7, 12-17]

Colonoscopy and Biopsy

Certain screening modalities, such as colonoscopy, sigmoidoscopy, CT colonography and to a lesser extent stool-based testing, will detect advanced adenomatous polyps, whereas colonoscopy is optimal for the detection of sessile serrated lesions (SSLs). Endoscopic removal of polyps reduces CRC incidence and CRC mortality.[5] Colonoscopy is regarded as the gold standard diagnostic technique for colorectal tumor detection to determine precisely the location of the tumor.

Pathology and Biomarker Test

Tumor biopsy remains the gold standard for initial pathologic diagnosis and molecular testing in CRC. Fresh tumor tissue is obtained from colorectal tumors, either by colonoscopic biopsy or surgery. The tumor is immediately fixated by using 10% formaldehyde buffering solution and made into paraffin blocks or formalin-fixed and paraffin-embedded tissues (FFPET). It is used to determine the histology of the tumor and to examine biomarker test. Immunohistochemistry test (IHC) is a special staining process performed on cancer tissue. IHC is used for the detection of chromosome instability (CIN), DNA-MMR defect (MSI status), and KRAS mutation status. PCR test is used for the detection of microsatellite Instability (MSI) and CpG Island Methylation Phenotype (CIMP).[3,7,9]

Laboratory Examination

Complete blood count, urinalysis, serum chemistries e.g., hepatic function panel, kidney function tests, etc. CEA tests is recommended before surgical operation and follow up after operation if there is a suspicion of cancer recurrence. An increase in the concentration of CEA after operation suggested of recurrence.

CT Scan or Magnetic Resonance Imaging (MRI)

If local or systemic metastasis CRC is suspected, the following radiologic studies may be obtained, such as CT scanning of the chest, abdomen and pelvis, MRI or trans rectal USG (TRUS) for rectal cancer. Diagnostic evaluation is conducted for localized staging of rectal cancer with TRUS: 80-95% accuracy of distinction between T1/2 vs T3 tumors. MRI is high degree of accuracy for prediction of circumferential resection margin with less operator dependent, and it allows for a study of stenotic tumors and pelvic adenopathy.[7,16]

BIOMARKERS IN CRC

As targeted therapies continue to emerge in the treatment of mCRC, knowledge and implementation of predictive and prognostic biomarkers will become increasingly important to ensure the best outcomes and to limit toxicity. Biomarker tests may impact selection of the most appropriate treatment strategy.[3,4,7,17-19] The application of novel molecular diagnostic test may lead to an improved survival of CRC patients.[20] The novel markers in conjunction with clinical and pathologic features have allowed for more individualized approaches to patients with CRC.[21]

The location, the stage of the tumor, and the result of biomarker tests can be used for

the assessment of the therapeutic approach. Some cancer treatments, including chemo therapies and targeted therapies, may only work for patient whose CRC have certain biomarkers.[3,4,17,18] Several biomarkers for mCRC include extended RAS (KRAS and NRAS) exons 2,3, and 4 mutations, BRAF V600E mutation, mismatch repair (MMR) or MSI and HER2 (human EGFR2) amplification. In addition, actionable gene fusions such as NTRK fusions or rearrangements (Neurotrophic Tropomyosin Receptor Kinases) are extremely rare but might represent a new target to improve outcomes in the setting. However, recent NGS (next-generation sequencing) approaches can detect all required types of genomic alterations, including amplification, fusions, and MSI.[18] MSI is a key biomarker in CRC, with crucial diagnostic, prognostic, and predictive implications.[22]

It is important for understanding the onset and the progression of CRC that can aid in the early detection of molecular markers and risks to improve the clinical care of CRC patients.[23] Gene mutations have the potential of disrupting several epigenetic patterns (DNA methylation, histone modification, and nucleosome positioning), and those epigenetic modifications can drive genome instability and mutagenesis (a crosstalk). Similarly, epigenetic inactivation of DNA MMR is often associated with genome instability and increased frequency of point mutations of cancer-related genes.[24]

The genes that are most commonly mutated in CRC patients include APC (about 80-82% of cases), TP53 (48-59%), KRAS (40-50%), and PIK3CA (14-18%). Some biomarkers are based on the mutational status of genes (KRAS, NRAS, BRAF) or associated with defects in the DNA mismatch repair system (dMMR). These defects are the underlying mechanism through which MSI status is determined.[17]

KRAS, BRAF BIOMARKER

Mutations in KRAS/NRAS exons 2 (codon 12 and 13), exon 3 (codon 59 and 61), and exon 4 (codons 117 and 146) are predicted due to lack of benefit for anti-EGFR mAb (such as cetuximab and panitumumab) treatments in mCRC. Patients with *RAS-Wild* Tumor who are left-sided demonstrated excellent outcomes with anti-EGFR-based therapy. Patients with BRAFV600E mutations demonstrated a markedly worse prognosis than non-BRAF V600E patients, and a number of sub analyses of mutation appear to suggest benefit from aggressive triplet-based therapy as a frontline therapy. Patients with BRAF V600E demonstrated a benefit in median progression free survival in the SWOG randomized clinical trial of vemurafenib/irinotecan/cetuximab in the second-line setting in comparison with irinotecan/cetuximab.[18,25] The BRAF gene is activated by mutation in 10-12% of all CRC and most frequently occur in codon 600 (BRAF V600).[17,25]

APC

Mutations in the APC gene occur in over 70% of sporadic CRCs, and they are the cause of the FAP cancer predisposition syndrome. The APC protein negatively regulates WNT signaling by facilitating the targeting of the transcription factor B-catenin for ubiquitin-mediated proteasomal degradation.[19] APC mutation in advanced state CRC had poorer overall survival. It can be used to predict the clinical outcome of CRC.[24]

MSI STATUS AND DMMR

Microsatellite Instability (MSI) status results from a deficient DNA mismatch Repair (dMMR) system commonly caused by the inactivation of the MMR genes (MLH1, MSH2, MSH6, PMS2, PMS1, and MLH3). MSI-high (MSI-H) is characterized by instability of two or more loci. MSI status can be determined by two distinct methods, immunohistochemistry analyses (IHC) or PCR based on five markers panel.[4,7,17,24]

MSI-H tumors can be observed in approximately 15% of all CRC patients. Of the 15%, 12% are associated with sporadic CRC, due to sporadic hypermethylation of the promoter of the MLH1 gene. The other 3% of MSI tumors are associated with Lynch syndrome, an inherited cancer syndrome associated with a genetic predisposition to CRC.[17] MSI/MMR testing should be performed in all patients diagnosed with CRC, and may be predicted with immunotherapy in the metastatic setting.[17,18,24]

CRC stage II MSI-H patients have a better prognosis and no beneficial effect of 5-FU.[22] This prognostic significance indicates the need to implement MSI screening for all resected stage II CRC patients. MSI status is less informative in stage III patients.[17] Emerging data suggest that tumors with dMMR or MSI-H respond better to immune check point inhibitors (ICIs).[17] The US FDA approved pembrolizumab, a monoclonal anti-PD1 antibody, for patients with MSI-H CRC. Additionally, Nivolumab and Iplimumab are approved options for refractory stage IV MSI-H patients, after prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan-based therapy.[17,18] MSI is a key biomarker in CRC, with crucial diagnostic, prognostic, and predictive implications. MSI-H status is associated with a better prognosis in early-stage CRC and a lack of benefit from adjuvant treatment with 5-fluorouracil (5FU) in stage II disease. MSI has emerged as a predictor of sensitivity to immunotherapy-base treatment.[22] Pemrolizumab is only effective in mCRC patients with MSI-H status.[25]

CIMP

Epigenetic instability in CRC is manifested as both hypermethylation of gene promoters that contain CpG island and global DNA hypomethylation. Aberrant DNA methylation is present in essentially all CRCs; however, there is a subset of CRCs (approximately 20%) that has an extremely high proportion of aberrantly methylated CpG loci. This class of CRCs has been characterized as having a CIMP. The discovery and classification of CIMP tumors have advanced our understanding of the molecular pathology of CRC, but it has not yet impacted clinical care.[19] CIMP status seems to overlap with BRAF mutations and MMR status. Thus, the independent prognostic value of CIMP needs to be validated.[17]

TP53

TP53 is the most frequent somatic gene mutation, and its mutational status has been associated with a positive response to adjuvant 5-FU therapy in stage III CRC patients. Further studies are necessary in order to determine the role of TP53 as a potential prognostic and predictive biomarker in CRC.[17] Mutations in the TP53 occur in about half of all CRCs, and these mutations promote the malignant transformation of adenoma. Like APC, TP53 is a key tumor suppressor gene that has been extensively studied in CRC, but it currently has no predictive or prognostic role in the clinical setting.[19] TP53 mutations or loss of function are reported in 50-75% of CRC cases.[23]

PI3K

Molecular lesions in the PI3K pathway, which in CRC are primarily mutations in *PIK3CA* and loss of PTEN protein expression. Mutations of genes in this pathway may have the potential to be used as predictive biomarkers for therapies that target the PI3K pathway, mammalian target of rapamycin (mTORC) pathway, as well as the MAPK pathway. Mutations in PI3K pathway genes are observed in up to 40% CRC patients.[19] It is difficult to evaluate the importance of PIK3CA as an independent pre dictive marker as PIK3CA mutations often co-occur with RAS or BRAF mutations.[17]

HER 2 ABERRATION

Human epidermal growth factor receptor 2 or HER2 (Errb2) is a transmembrane receptor of the EGFR family and its activation leads to cell proliferation and apoptosis inhibition. The frequency of HER2 overexpression is reported to be around 5% with ERRB2 amplifications reported in 5.5% of mCRC.[17,25] The implementation of HER2 assessment in daily practice might provide useful information for guiding therapy decision.[17] Several studies suggest the amplifications of ERBB2 negatively predict efficiency and are associated with development of resistance to anti-EGFR therapy.[17,18]

CONSENSUS MOLECULAR SUBTYPES

In late 2016, a large consortium of groups working on CRC combined their efforts and identified four molecular subtypes based on multi gene arrays, which were conserved across all examined studies. These subtypes are referred to as CMS1 (MSI-immune subgroup representing

14% of CRC cases), CMS2 (canonical subgroup accounting for 37% cases), CMS3 (metabolic representing 13% of CRC patients) and CMS4 (mesenchymal representing 23% of CRC cases). CMS subtypes primarily show an association with clinical outcomes. The clinical impact of the identification of these subtypes remains relatively limited.[17,23,25]

MicroRNAs

MicroRNA (miRNAs) are considered to be exceptional biomarkers due to their involvement in multiple physiologic pathways and their stability in paraffin-embedded tissue (FFPET), which is an important factor for the translation of biomarkers into the clinics. miRNAs play an important role in the regulation of intracellular processes via the post-transcriptional regulation of gene expression.[17] Several specific miRNAs were identified as predictive or prognostic biomarkers in CRC.[20, 25] Numerous miRNAS have been reported in tumor specimens from CRC patients, and several representative miRNAs have been identified in tumor tissues that have prognostic value and response to anti-cancer drugs in CRC patients.[25,26] Despite the numerous studies of miRNAs and extensive analyses of their expression, the role and function of many individual miRNAs in CRC remains poorly understood.[27]

TUMOR LOCATIONS

The most interesting concept in CRC is the impact of the primary tumor location. Colon is known to have two distinct embryological origins, namely the midgut for the proximal colon and the hindgut endoderm for the distal colon. Additionally, the two parts of the colon have different blood supplies, distinct microbiome populations and are associated with different biological features. Proximal colon cancer shows a worse prognosis than distal colon cancer. Anti-EGFR therapy should be limited to distal colon cancer with KRAS wild type.[17] Primary tumor location affects response to targeted therapy and is essential for the treatment selection for RAS wild type mCRC.[18]

A study on molecular biomarker in CRC based on three locations (proximal colon, distal colon and rectum) was published (Effendi et al., 2013). In this study, tumor tissues of CRC patients from three locations were examined by IHC and PCR test. The protein expressions were determined by IHC for APC, dMMR (MLH1, MSH2, MSH6, and PMS2), while microsatellite instability-high (MSI-H) by PCR was based on 5 markers of BAT25, BAT26, D2S123, D5S346, D17S250, known as Bethesda panel. MSI-H was considered if there were ≥ 2 of abnormal markers.[4,7,24] There were differences in the characteristics of CIN, MMR, and MSI-H found in colorectal cancer patients based on different locations. The MLH1 protein expression negative was prominent in proximal colon cancer, MSH6 in distal and rectal cancer, and APC in distal colon cancer respectively. The proportion of MSI-H displayed a tendency to occur in proximal rather than in distal colon or rectal cancer. Nevertheless, these findings suggest that the underlying carcinogenic pathway or molecular backgrounds differ according to the cancer locations among CRC patients in this region. The CRC in each location has its specific molecular characteristics.[3,4,7]

Right colon cancer or proximal colon cancer had better outcome at stage II in comparison with Left CC, and it had better outcomes at stage I and II in comparison with rectal cancer. In other words, Right CC was associated with a relatively favourable outcome in an early-stage disease, but had an opposite outcome in regional and metastatic disease. In this case, tumor heterogeneity was considered as the main potential reason. Tumor phenotypes may vary depending on the process of tumor infiltration and metastasis.[14]

Cancer Stem Cells (CSCs)

CSCs have been put forward to be one of the determining factors that contribute to intra-tumor heterogeneity and the potential implications for CRC therapy.[27] CSCs can escape the chemotherapy and differentiate into mature cancer cells, resulting into cancer recurrence and metastasis. Therefore, development of therapy targeting CSCs has a¬therapeutic potential, and it is important to identify approaches in combination with conventional therapy for

targeting and eradicating CSCs.[3,4,9,28-30]

TREATMENT

Most CRC patients are treated with surgery to remove the tumor tissue, and some of the CRC patients recurred. Chemotherapy used as adjuvant or neoadjuvant therapy also presents several problems, in which these treatments are useless in tumor cells with chemo-resistance. Despite advanced treatment strategies, CRC is rarely cured completely due to recurrence. Chemotherapy can only shrink tumors by killing the active tumor cells but miss the quiescent colorectal cancer stem cells (CSCs). This leads to resistance and relapse, and usually includes systemic and local toxicity of chemotherapy. CSCs are considered as the origin of tumorigenesis, development, metastasis and recurrence in theory.[3,8,9]

Surgery is the primary treatment for CRC, that it is limited to the colon or rectum. It aims to remove cancerous tissue of an early stage cancer, including tumors and nearby lymph nodes, preventing the cancer from spreading. In the later stages**,** surgery cannot stop the cancer from spreading.

Systemic therapies for localized and advanced CRC include chemotherapy, targeted therapy, immune therapy, and a newly developed therapy. Systemic therapy for CRC aims to downsize the primary tumor or metastases in order to convert them to a resectable status and increase progression-free survival.

Chemotherapy drugs destroy cancerous cells throughout the body. It may shrink a tumor before surgery. It can also help relieve symptoms in the later stages. Chemotherapy can have widespread adverse effects, as it targets both cancerous and healthy cells.

Targeted therapy involves taking drugs that target specific protein to slow or prevent the growth of cancer cells. The adverse effects are usually less severe than those of chemotherapy because these drugs only target specific cells.

Immunotherapy can have possible adverse effects include an autoimmune reaction, in which the body mistakenly attacks its own cells. If CRC spreads to organ beyond the colorectal, progressing to stage 4, it is not possible to cure it.

Recently numerous *newly developed therapies* are available. Other option for stage 4 CRC may include: surgery to remove a blockage, radiation therapy or chemotherapy to reduce the size of tumors, pain relief, treatment for side effects of medication, and counseling. Therapeutic management should involve a multidisciplinary approach that includes diagnostic accuracy, surgical technique (high quality surgery), biomarker test, optimal selection of drug treatment or procedure and informed consent.[16,31-33]

Colon cancer

a. Stage I: Surgery
b. Stage II-III: Surgery ± adjuvant chemotherapy
c. Stage IV: Chemotherapy ± palliative surgery.

Rectal cancer

a. Stage I: Surgery (local excision) or total mesorectal excision (TME).
b. Stage II-III: Neoadjuvant chemoradiation followed by resection, followed by adjuvant chemotherapy.
c. Stage IV: Chemotherapy ± surgery.

Surgery is also performed if there is a perforation or blockage due to a tumor.

Sometimes endoscopic stent placement is required before surgery for partial obstruction due to CRC.[16, 31-33]

Chemotherapy for advanced CRC and metastasis:[16]

a. 5-FU/Leucoferin+ Oxaliplatin (Folfox),
b. 5-FU/LV+ irinotecan (Folfiri), or
c. Capecitabin + Oxaliplatin (CapeOx).

TARGETED THERAPY

Targeted therapies are recommended for patients with KRAS/NRAS/BRAF mutated tumors, or wild-type tumors, HER2-amplified tumors and NTRK gene fusion-positive tumors. Development and approval of novel targeted therapies such as monoclonal antibodies against EGFR and VEGF have significantly increased the median survival of CRC patients with advanced or metastatic disease.

Monoclonal antibodies against EGFR (cetuximab or panitumumab) are recommended for patients with KRAS/NRAS/BRAF wild-

type tumors. There are no roles for anti EGFR therapy in KRAS mutation CRC, as well as for dual anti EGFR and anti VEGF combination therapy.[16, 31,33-36]

Targeted cytotoxic drugs against colorectal CSCs marker research will provide more effective therapeutic results as well as reduce resistance and recurrence.[3,37,38]

CR-CSCS are defined with a group of cell-surface markers, such as CD44, CD133, CD24, epithelial cell adhesion molecule (EpCAM), LGR5, and acetaldehyde dehydrogenase (ALDH). They are highly tumorigenic, aggressive, radioresistant and chemoresistance and thus are critical in the metastasis and recurrence of CRC. Therefore, targeting CR-CSCs may become an important research direction for the future cure of CRC.[39,40] The biological activities of CSCs are regulated by several pluripotent transcription factors, such as OCT4, Sox2, Nanog, KLF4, and MYC. In addition, many intracellular signaling pathways, such as Wnt, NF-kB(nuclear factor-kB), Notch, Hedgehog, JAK-STAT (Janus kinase/signal transducers and activators of transcription), PI3K/AKT/mTOR (phosphoinositide 3-kinase/AKT/mammalian target of rapamycin), TGF(transforming growth factor)/ SMAD, and PPAR (peroxisome proliferator-activated receptor), as well as extracellular factors, such as vascular niches, hypoxia, tumor-associated macrophages (TAM), cancer-associated fibroblasts, cancer-associated mesen chymal stem cells, extracellular matrix, and exosome, have been shown to be very important regulators of CSCs.[41]

Tumor microenvironment (TME), contains both cellular components with cancerous and non-cancerous cells such as stromal myofibroblast, endothelial cells, immune cells and cancer-associated fibroblast (CAFs), and non-cellular components including extracellular matrix (ECM), cytokines, growth factors and extracellular vesicles. In the tumor stroma, CAFs secrete the cytokines CXCL1 and CXCL2 as well as the interleukin-6, which promote angiogenesis and tumor progression.[42,43] CSCs reside in anatomically specialized regions of the TME, known as CSC niche, which retain their properties and protect them from anticancer drugs, contributing to their enhanced resistance to treatment. TME and metabolic plasticity may also be involved in therapeutic failure by imposing selective pressures on CSCs that lead to chemoresistance and cancer progression. Therefore, the development of new therapies targeting CSCs taking into account the TME and tumor metabolism, represents an interesting approach to overcome resistance to therapies.[42, 43]

CSCs are thought to be responsible for tumor initiation and dissemination, drug and radiation resistance, invasive growth, metastasis, and tumor relapse. Specific pheno types could be used to distinguish CSCs from non-CSCs. CSCs are modified by the aberrant expression of several microRNAs.[44] Thus, it is very difficult to target CR-CSCs. Targeting cytotoxic drugs to CR-CSCs with the help of stem cell surface markers provides a useful method to treat CRC. Also, the use of inhibitors targeting drug-detoxifying enzymes, drug-efflux pumps, or transcription factors of CSCs represents a novel approach to target the CSCs and reduces cancer recurrence and metastasis.[7, 45]

Immunotherapy

Immune checkpoint inhibitors (ICIs) are a type of immunotherapy often made from antibodies. ICIs target co-inhibitory receptors, such as CTLA-4 and programmed cell death protein 1 (PD-1) on T cells and other immune cell sub populations, or their ligands, such as PD1 ligand 1 (PD-L1) on tumor cells and various immune cells. In CRC, it has been shown that only patients with the subset of dMMR or MSI-H tumors are likely to respond to treatment with ICIs.[46-48]

Therapeutic approaches for the treatment of CRC include surgery (surgical resection), local therapies for metastatic disease, a systemic therapy comprising chemotherapy, targeted therapy and immunotherapy, and palliative chemotherapy.[42]

Surgery can be associated with neoadjuvant therapy in order to shrink tumor mass and fascilitate medical operation and/or with adjuvant therapy to limit cancer recurrence. Importantly, neoadjuvant chemotherapy, possibly coupled with radiotherapy, is mainly indicated for rectal cancers.[42.] Treatment options and

recommendations depend on several factors. These factors‒include: the patient's overall health, possible side effects, the type, the size and the stage of the tumor, the location of the tumor, and its mutational and MMR status, or biomarkers.[42]

The lines of treatment in mCRC currently involve a combination of targeted therapies that inhibit the EGFR (cetuximab and panitumumab), or angiogenesis (bevacizumab, regorafenib, aflibercept, or ramucirumab), together with chemotherapy (5-fluorouracil, irinotecan, oxaliplatin, Folvox, Folfiri, or CapeOx).[46]

Systemic therapies for localized and advanced colorectal cancer[42]

1. Chemotherapy:
   - 1a 5-Fluorouracil (antimetabolite).
   - 1b. Capecitabine (antimetabolite).
   - 1c Irinotecan (Topoisomerase inhibitor).
   - 1d. Oxaliplatin (Alkylating agent).
   - 1e Trifluridine/Tipiracil (Nucleoside analog / thymidine phosphorylase inhibitor)

   [1a to 1d: Recommendations for: Localized and advanced tumors].
2. Targeted therapy:
   - 2a. Bevacizumab (mAb anti-VEGF-A).
   - 2b. Regorafenib (Multikinase inhibitor targeting e.g. VEGFR and BRAF).
   - 2c. Aflibercept. (Recombinant fusion protein blocking VEGF -A/B).
   - 2d. Ramucirumab (mAb anti-VEGFR-2.

   [*2a to 2d: Recommendations for: KRAS/ NRAS/BRAF Mutated tumors*].
   - 2e. Cetuximab (mAb anti-EGFR).
   - 2f. Panitumumab (mAb anti-EGFR).

   [2e to 2f: Recommendations for: KRAS/ NRAS/BRAF Wild-type tumors]
3. Immunotherapy:
   - 3a. Pembrolizumab (mAb anti-PD-1).
   - 3b. Nivolumab (mAb anti-PD-1)
   - 3c. Iplimumab (mAb anti- CTLA-4).

   [3a to 3c: Recommendations for: MSI-High tumors].
4. Newly developed therapy.
   - 4a. Vemurafenib (BRAF inhibitors).
   - 4b. Dabrafenib. (BRAF inhibitors).
   - 4c. Encorafenib. (BRAF inhibitors).
   - 4d. Trametinib (MEK inhibitors).
   - 4e. Binimetinib (MEK inhibitors).

   [*4a to 4e: Recommendations for: BRAF V600E mutated tumors*].
   - 4f. Trastuzumab. (mAb anti HER2).
   - 4g. Pertuzumab. (mAb anti HER2).
   - 4h. Lapatinib. (Dual HER2/EGFR inhibitor)

   [*4f to 4h: Recommendations for: HER2 amplified tumors*].
   - 4i. Larotrectinib. (TRK inhibitors)
   - 4j. Entrectinib. (TRK inhibitors).

   [*4i to 4j: Recommendations for: NTRK gene fusion-positive tumors*].

* monoclonal antibody anti-programmed cell death receptor-1 (mAb anti-PD-1)

* anti -cytotoxic T lymphocyte associated antigen -4 (anti- CTLA-4)

* TRK- tropomyosin receptor kinases.

* MEK-Mitogen-activated kinases.

* NTRK- neurotrophic tropomyosin kinase.

CONCLUSION

Clinical signs and symptoms of CRC vary, and they are related to the location of cancer whether in proximal, distal colon or rectum, the tumor size, and the stage of CRC. Colonoscopy is the gold standard diagnostic tools, and to prevent CRC by screening and removing premalignant lesions. Biomarkers will give the information on prognostic value, serving as predictive marker for the possibility of response to chemotherapy, biological target agent, immunotherapy, newly developed therapy or targeted therapy. The approved target therapy related to the markers can be used for the selection of the treatment. The more precisely targeted therapies which can selectively target CSCs but spare normal stem cells are necessary and further research on the Colorectal-CSCs markers is greatly needed. The role of the CSCs surface markers as well as targeted therapies to CR-CSCs are currently being studied by various research centers.

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How to Diagnose, Treat, and Monitor Treatment Response in Patients with Multiple Myeloma

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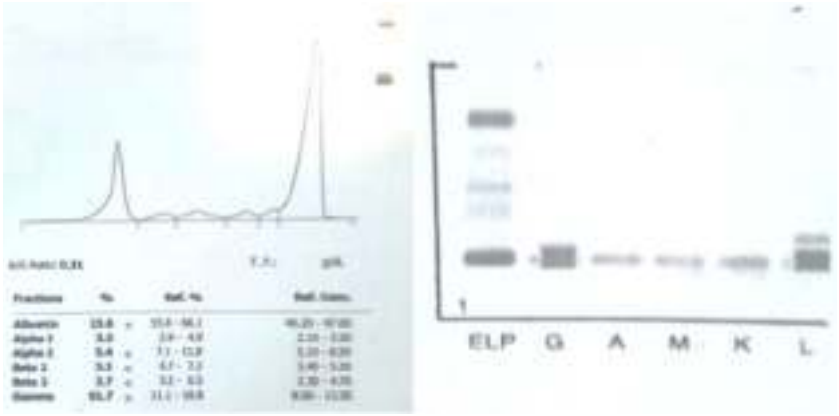

Figure 1. Serum protein electrophoresis and immunofixation showed the presence of gammopathy IgG and lambda light chain

Figure 2. Skeletal radiography: multiple osteolytic lesions in calvaria.

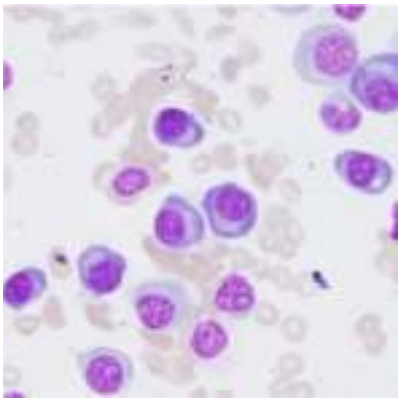

Figure 3. Percentage of plasma cells in the bone marrow in the patient: 46%.

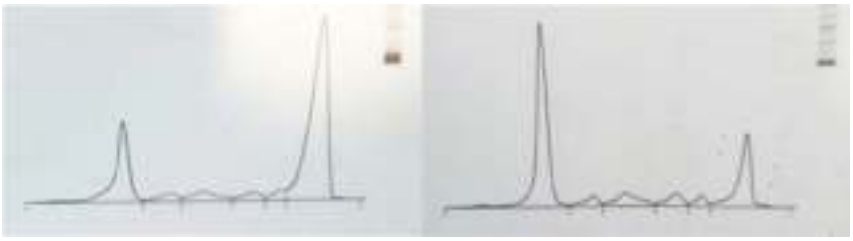

Figure 4. Response of treatment after four cycles of induction VCD

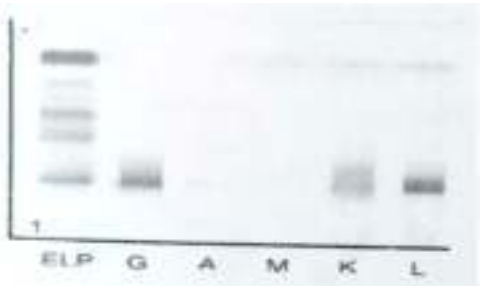

Figure 5. Immunofixation still detected IgG and lambda light chain after four cycles of induction VCD

Multiple myeloma (MM) is a B-cell malignancy characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein production in the serum, and organ dysfunction.[1] It is part of a disease spectrum called plasma cell disorders,[2] and to establish the diagnosis, a bone marrow biopsy should be conducted with clinical signs of end-organ damage and/or significantly elevated monoclonal protein (M-protein). MM can also be diagnosed without end-organ damage when certain conditions are met since the International Myeloma Working Group (IMWG) has come up with new diagnostic criteria for multiple myeloma.[2]

Treatment for all patients with MM aims to enhance the depth and duration of response while limiting drug toxicity to lengthen survival, improve quality of life, alleviate symptoms and prevent further organ damage.[3] Development of new drugs has improved the survival of patients[4] Available tests for monitoring of patients with MM most often include assessments of monoclonal paraprotein and serum-free light chain levels with bone marrow examination, which directly identifies the level of malignant plasma cells.[5]

A 40 years old male suffered from back pain and fatigue for 6 months. Physical examination only showed pale conjunctiva, indicating anemia, which was confirmed by test results with a hemoglobin level of 8.5 g/dL. In addition, there were slightly elevated blood ureum 58 mg/dL (normal value: 20-50 mg/dL), serum creatinine 1.73 mg/dL (normal value: 0.7-1.2 mg/dL), and low serum calcium level 7.8 mg/dL (normal value: 8.5-10.5 mg/dL). The value of elevated total protein, low albumin, and highly elevated serum globin was 14.1 g/dL (normal value: 6.6-8.7 g/dL), 2.8 g/dL (normal value: 3.4-4.8 g/dL), and 11.3 g/dL (normal value: 1.5-3.0 g/dL), respectively. Serum protein electrophoresis and immunofixation confirmed the presence of IgG and lambda light chain gammopathy. Meanwhile, the level of serum IgG, free light chain (FLC) kappa, FLC lambda was 10,741 (normal value: 800-1,813 mg/dL), 17.36 ng/L (normal value:3.3-19.4 ng/L), and 1,650 ng/L (normal value: 5.71-26.3 ng/L), respectively, with serum free light chain ratio = 95. Multiple osteolytic lesions in the calvaria and compression fractures in the 6^{th}, 9^{th}, 11^{th}, 12^{th}, and 13^{th} thoracic vertebrae were seen on skeletal radiography. Bone marrow aspiration showed the presence of plasma cells comprising 46% of all cells.

The Revised IMWG 2014 updated criteria for the diagnosis of multiple myeloma has developed the diagnostic criteria of: clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more myeloma defining events:[2,6]

a. Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, also known as the "CRAB" mnemonic: hypercalcemia (serum calcium >11 mg/dL), renal insufficiency (serum creatinine >2 mg/dL or creatinine clearance <40 mL per min), anemia (Hemoglobin <10 mg/dL), or bone lesions [on skeletal radiography, computed tomography (CT), or positron emission tomography (PET) -CT].
b. One or more of the following malignancy biomarkers: clonal plasma cells in bone marrow ≥60%, ratio of serum FLC ≥100 (involved FLC≥100 mg/dL), or >1 focal lesion found by magnetic resonance imaging (MRI).[2]

The Revised IMWG 2014 criteria established the diagnosis of multiple myeloma in this patient based on the ≥10% percentage of bone marrow plasma cells with organ damage anemia and lytic bone lesions. European Hematology Association and European Society for Medical Oncology (EHA-ESMO) Clinical Practice Guidelines for diagnosis, treatment, and follow-up recommend three-drug combination VRd (Bortezomib, lenalidomide, and dexamethasone), VTD (Bortezomib, thalidomide, and dexamethasone), or VCD (Bortezomib, cyclophosphamide, and dexamethasone) as induction chemotherapy regimen. These were followed by stem cells mobilization, harvesting, and High Dose Melphalan (HDM) 200 mg/m^2 with autologous stem cell transplantation (ASCT).[5] Furthermore, the patient's induction chemotherapy regimen was administered with a three-drug combination of Bortezomib, cyclophosphamide, and dexamethasone (VCD) for four cycles.

The diagnostics now available to evaluate the patient's response to therapy for MM include periodic evaluations of M-protein and serum FLC levels, immunofixation, and bone marrow examination to detect residual malignant plasma cells. However, serological/morphological complete response (CR) may still underestimate residual disease. This is because the IMWG has incorporated Minimal Residual Disease (MRD) assessed by multicolor immunofluorescence flow cytometry and gene sequencing into MM response criteria with the absence of bone disease on PET-CT scanning.[1,5,7] The treatment response after four cycles of VCD was partial response (PR) since the immunofixation was still detected. Plasma cells in the bone marrow were 7.5%, and the patient achieved normal measurable serum IgG and lambda light chain: IgG 1,500 mg/dL (normal value: 800-1,813 mg/dL) and lambda 15.5 ng/L (normal value: 5.71-26.3 ng/L).

This VCD regimen, also known as CyBorD, has been utilized as the standard induction in transplant-eligible newly diagnosed MM. The combination therapy has shown good outcomes when continued with ASCT.[8] The patients were promoted to continue with HDM and ASCT after the discussion. The patient evaluated in this research is a good candidate for transplantation since he is young and free of comorbidities. The preparation for transplantation requires multi-disciplinary team coordination and support from the healthcare facility. The possibility of mortality and morbidity due to post-transplant complications should also be communicated effectively with the patient and families. Additionally, this medical illustration shares the experience of diagnosing, treating, and monitoring the therapeutic response of patients with newly diagnosed multiple myeloma.

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The Effect of Statin Therapy on Mortality in Adult Patients with Liver Cirrhosis: An Evidence-Based Case Report

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ABSTRACT

***Background*:** *Liver cirrhosis causes over one million deaths annually worldwide, but its prognosis varies depending on the presence of complications and decompensating events. Reduction of portal pressure is associated with a reduced risk of mortality in cirrhotic patients. Statin therapy has successfully reduced portal pressure in previous studies, but its effects on overall mortality are unclear. This report aims to determine whether statin therapy significantly affects mortality in patients with liver cirrhosis.* ***Methods*:** *A comprehensive literature search was conducted using five electronic databases: PubMed, Scopus, Embase, Ovid MEDLINE, and Web of Science. Meta-analyses, randomized controlled trials (RCTs), and cohort studies were selected based on pre-set inclusion and exclusion criteria. The quality of selected studies was evaluated using critical appraisal tools developed by the Center for Evidence-Based Medicine.* ***Results*:** *One meta-analysis, one RCT, and one retrospective cohort study were included in this report. The meta-analysis and cohort study were of good quality and reported significantly reduced mortality with statin therapy in cirrhosis patients. However, the RCT had poor validity and did not report a statistically significant difference in mortality between the intervention and control groups. The survival benefits of statins may be limited to Child–Pugh A and B patients only, but this requires confirmation in a larger population of Child–Pugh C patients.* ***Conclusion*:** *Statins potentially reduce mortality in patients with liver cirrhosis, but more evidence is required before they can be widely recommended in clinical practice for this indication.*

Keywords*: Liver cirrhosis, fibrosis, evidence-based medicine, portal pressure, statins.*

INTRODUCTION

Liver cirrhosis is advanced stage liver disease resulting from chronic damage and necroinflammation of hepatic tissue due to several etiologies, such as viral hepatitis and alcohol-induced toxicity. It is characterized by the presence of regenerative nodules surrounded by networks of thick fibrotic septae, eventually leading to intrahepatic vascular disturbances and loss of hepatocellular function.[1] Liver cirrhosis is the 12th most common cause of death worldwide, claiming more than one million lives annually.[2] Despite this large disease burden, the prognosis of cirrhosis is highly variable; its one-year mortality ranges from 1– 57% depending on the presence of complications and decompensating events.[3]

Portal hypertension is commonly found in cirrhotic patients and is responsible for many complications of cirrhosis.[1] It drives the formation of gastroesophageal varices, and variceal bleeding is associated with a

six-week mortality of 10–20%.[4] It is also responsible for portosystemic shunting of blood, which contributes to the development of hepatic encephalopathy.[5,6] The hyperdynamic circulation in cirrhosis is associated with the development of hepatorenal syndrome and ascites.[1] Decompensation of cirrhosis is defined by the presence of severe complications, including gastrointestinal bleeding, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy, and is associated with a poor prognosis.[7]

The progression of cirrhosis can be slowed by lifestyle modifications and pharmacological intervention.[1] An important pharmacotherapeutic target in liver cirrhosis is reduction of portal hypertension. A previous meta-analysis reported that a reduction in the portal pressure by ≥ 20% significantly reduces mortality in cirrhotic patients (pooled odds ratio (OR): 0.39, P = 0.012).[8] Current guidelines support the use of non-selective beta blockers (NSBBs) to reduce portal hypertension.[4] However, NSBBs are associated with low hemodynamic response rates and systemic adverse effects.[9-11] Hence, there is a need for other pharmacological agents that can reduce portal pressure. Studies have demonstrated that statins (HMG-CoA reductase inhibitors) can increase intrahepatic nitric oxide (NO) production through upregulation of the transcription factor Krüppel-like factor 2 (KLF-2).[12–14] Reduced intrahepatic NO production by the sinusoidal endothelium contributes to portal hypertension in cirrhosis.[12] Abraldes et al demonstrated that simvastatin increased endothelial nitric oxide synthase (eNOS) expression and activation in cirrhotic rats.[12] Zafra et al reported increased post-prandial hepatic NO products in simvastatin-treated cirrhotic patients.[13] Previous randomized controlled trials (RCTs) on cirrhotic patients report a greater reduction in the hepatic venous pressure gradient (HVPG) with simvastatin administration compared to placebo.[15,16] Aside from reducing portal hypertension, statins are potentially beneficial in cirrhosis by reducing hepatic stellate cell activity and through their immunomodulatory and anti-neoplastic properties. These protective mechanisms are summarized in **Figure 1**.[17,18]

Although statin therapy can reduce portal pressure and exert other potential benefits in liver cirrhosis, it is unclear whether it can improve overall survival in this patient group. Current guidelines do not recommend statin therapy for patients with liver cirrhosis.[4] The aim of this report was to evaluate whether statin therapy can reduce mortality and improve overall survival in adult patients with confirmed liver cirrhosis.

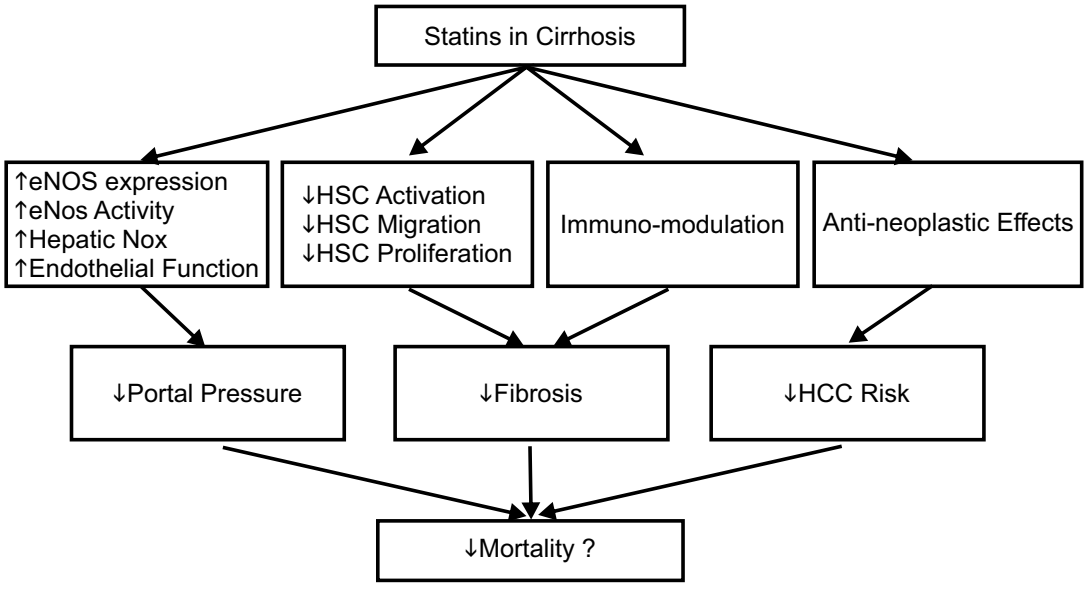

Figure 1. Biological mechanisms of the benefits of statin therapy in cirrhosis[17,18]

CASE ILLUSTRATION

A 39-year-old male patient was admitted with a one week history of massive ascites prior to admission. The patient first experienced ascites two months before admission. At this time, he was diagnosed with hepatitis C with a viral load of three million copies and liver cirrhosis based on abdominal ultrasonography (USG). Since then, the patient was on direct-acting antiviral therapy (sofosbuvir + daclatasvir). One month before admission, esophagogastroduodenoscopy showed esophageal varices (grade 2), large gastric fundal varices, and portal hypertensive gastropathy. At that time, the patient underwent therapeutic paracentesis, but the ascites returned after approximately one week. Since then, the patient experienced refractory ascites and underwent therapeutic paracentesis a total of three additional times with the ascites recurring shortly after each session.

On physical examination, the patient was found to have icteric skin and sclera. The conjunctiva and oral mucosa were pale. The abdomen appeared distended, with distension of the abdominal wall veins. Shifting dullness and fluid wave tests were positive. Bilateral pitting edema was found on the lower extremities. Laboratory examinations showed hyperbilirubinemia (4.41 mg/dL), hypoalbuminemia (2.07 g/dL), hyponatremia (126.0 mEq/L), hyperkalemia (7.0 mEq/L), and reduced kidney function (eGFR: 57.0 mL/min/1.73m^3). Abdominal USG suggested hepatic cirrhosis, splenomegaly, and ascites. The patient underwent therapeutic paracentesis twice during his hospital stay, with persistent massive ascites post-paracentesis.

The patient denied any history of hematemesis, melena, loss of consciousness, or alteration in his behavior or mental state. Based on the available data, the patient's liver cirrhosis was classified as Child-Pugh class C, indicating a poor prognosis and a higher risk of mortality. Currently, pharmacological options that can reduce the risk of mortality in adults with liver cirrhosis are limited. Studies suggest that statins can improve portal hypertension in this population, but their effects on mortality are not well understood.

CLINICAL QUESTION

It is unclear whether statin therapy can reduce mortality in adults with liver cirrhosis, such as in the patient described above. Thus, the following clinical question arose: What is the effect of statin therapy on mortality in adult patients with liver cirrhosis? The patients, intervention, comparison, and outcome (PICO) format for this question was as follows:

- Patients (P): Adults with Liver Cirrhosis
- Intervention (I): Statin Therapy
- Comparison (C): No Statin Therapy
- Outcome (O): Mortality/Survival

METHODS

Search Strategy

To answer the clinical question, a comprehensive literature search was conducted in July 2019 using the following databases: PubMed, Scopus, Embase, Ovid MEDLINE, and Web of Science. The keywords used for the search are presented in **Table 1**.

Eligibility Criteria and Article Selection

The following inclusion criteria were applied in this study: 1) clinical studies on adult patients with confirmed liver cirrhosis; 2) comparison between patients with and without statin therapy; and 3) mortality or survival as an outcome measure. Studies without a specific analysis for baseline cirrhotic patients or studies including only hepatocellular carcinoma (HCC) patients were excluded. The types of studies included were meta-analyses, systematic reviews, RCTs, and cohort studies. Inclusion was not restricted by year of publication, sample size, or language.

Critical Appraisal

The quality of selected studies was evaluated using critical appraisal tools available from www.cebm.net developed by the Center for Evidence-Based Medicine (CEBM) at the University of Oxford.[19] Critical appraisal was conducted by both authors independently. Any differences in judgement were discussed among both authors before the final decision was made.

Data Extraction

The data extracted from each study included the study population, details of statin therapy, and

Table 1. Electronic databases and keywords used in the search.

Database Used	Search Strategy and Keywords Used
PubMed	(((cirrhosis[Title/Abstract] OR cirrhotic[Title/Abstract])) AND (mortality[Title/Abstract] OR survival[Title/Abstract] OR prognosis[Title/Abstract] OR death[Title/Abstract])) AND (statin[Title/Abstract] OR atorvastatin[Title/Abstract] OR fluvastatin[Title/Abstract] OR simvastatin[Title/Abstract] OR lovastatin[Title/Abstract] OR pitavastatin[Title/Abstract] OR pravastatin[Title/Abstract] OR rosuvastatin[Title/Abstract])
Scopus	TITLE-ABS-KEY (cirrhosis OR cirrhotic) AND TITLE-ABS-KEY (mortality OR survival OR prognosis OR death) AND TITLE-ABS-KEY (statin OR atorvastatin OR fluvastatin OR simvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin)
Embase	1. (cirrhosis or cirrhotic).ab,kw,ti. 2. (mortality or survival or prognosis or death).ab,kw,ti. 3. (statin or atorvastatin or fluvastatin or simvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin).ab,kw,ti. 4. 1 and 2 and 3
Ovid MEDLINE	1. (cirrhosis or cirrhotic).ab,kw,ti. 2. (mortality or survival or prognosis or death).ab,kw,ti. 3. (statin or atorvastatin or fluvastatin or simvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin).ab,kw,ti. 4. 1 and 2 and 3
Web of Science	#1: ALL=(cirrhosis OR cirrhotic) #2: ALL=(mortality OR survival OR prognosis OR death) #3: ALL=(statin OR atorvastatin OR fluvastatin OR simvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin) #4: #1 AND #2 AND #3

survival outcomes. Both authors conducted data extraction independently. Any disagreements were discussed among both authors before the final decision was made.

RESULTS

Search Results

Figure 2 shows a Preferred Reporting Items for a Systematic Review and Meta-Analysis style flowchart outlining the sequential steps applied in the selection of studies. A total of eight articles were considered relevant based on the selection criteria. Of these, the meta-analysis by Kim et al included five of the other relevant articles identified.[20] Hence, this meta-analysis, along with an RCT by Bishnu et al[21] and a retrospective cohort study by Kaplan et al[22] were selected for further analysis.

Kim et al conducted a meta-analysis of one RCT and four retrospective cohort studies.[20] Bishnu et al randomized 30 consecutive patients with confirmed liver cirrhosis to receive either NSBBs with atorvastatin or NSBBs alone.[21] The retrospective cohort study by Kaplan et al evaluated the effect of statin therapy on mortality in patients with confirmed liver cirrhosis. Their cohort consisted of 21,921 patients receiving statin therapy at baseline and 53,063 patients without baseline statin therapy (i.e., a statin naïve group). Within the statin naïve group, the authors conducted a subgroup analysis where each statin initiator (i.e., each patient who started statin therapy during follow-up) was matched and compared to two statin non-initiators (i.e., patients never treated with statins throughout follow-up). From this subgroup analysis, information about the effect of cumulative statin therapy was extracted. Comparisons in mortality between statin non-initiators and statin initiators at baseline were also extracted.[22]

Critical Appraisal

All three selected articles were critically appraised for validity, importance, and applicability using tools developed by the CEBM.[19] Since there were different types of studies, appropriate tools were selected for each study. The validity of selected studies is presented in **Table 2**.

The studies conducted by Kim et al and Kaplan et al were well designed and sufficiently valid.[20,22] However, the RCT by Bishnu et al had reduced validity and was prone to significant bias.

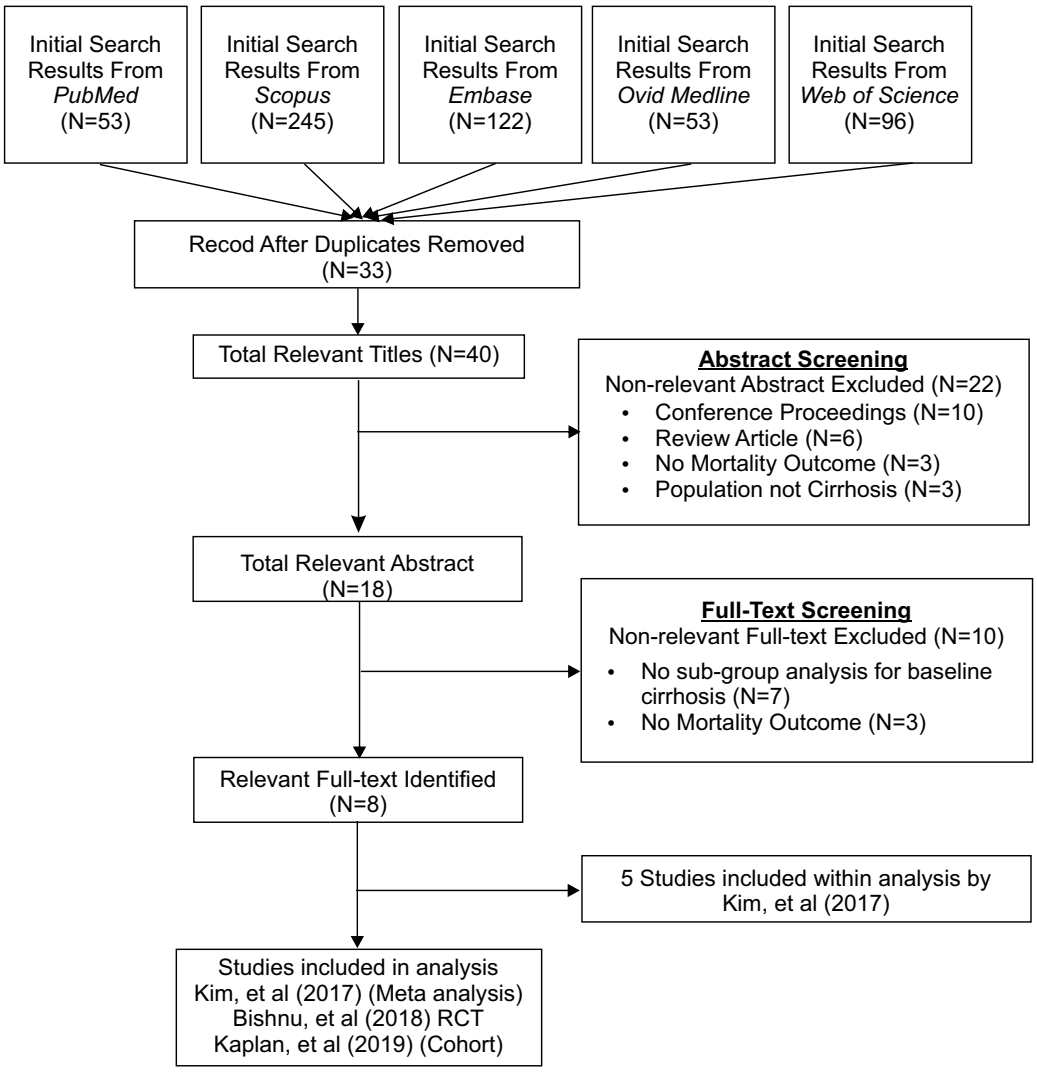

Figure 2. The results of electronic database searches and study selection.

Table 2. Validity of selected studies.

Kim et al (Meta-Analysis)		Bishnu et al (RCT)		Kaplan et al (Retrospective Cohort)	
Was the main question being addressed clearly stated?	Yes	Was the assignment of patients to treatments randomized?	Yes	Was the defined representative sample of patients assembled at a common point in the course of their disease?	Yes
Is it unlikely that important, relevant studies were missed?	Yes	Were the groups similar at the start of the trial?	Yes	Was patient follow-up sufficiently long and complete?	Yes
Were the criteria used to select articles appropriate?	Yes	Aside from the allocated treatment, were groups treated equally?	Yes	Were outcome criteria either objective or applied in a 'blind' fashion?	Yes
Were the included studies sufficiently valid for the type of question asked?	Yes	Were all patients who entered the trial accounted for? And were they analyzed in the groups to which they were randomized?	No	If subgroups with different prognoses were identified, did adjustment for important prognostic factors take place?	Yes
Were the results similar from study to study?	Yes	Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No		

In this open-label trial, neither the investigators nor the participants were blinded to group allocation. In addition, 23.3% of this study's population was lost to follow-up (3/15 in the control group and 4/15 in the treatment group) without an intention-to-treat analysis.

According to the CEBM critical appraisal tools, the importance of each study refers to the size and precision of treatment effects, which is denoted by a relative risk (RR) or hazard ratio (HR) and confidence intervals (CIs). This information is presented in the Data Extraction section. All three studies are applicable to the patient described in this case report, as they only included patients with confirmed liver cirrhosis. Treatment with statins is feasible in clinical practice, as these drugs are widely available at a relatively low cost.

Data Extraction

From each study, data about the study design and population, statin therapy, and mortality outcomes were extracted. These data are presented in **Table 3**.

DISCUSSION

A total of three studies answering the clinical question were identified. The meta-analysis by Kim et al[20] represents the highest level of evidence and was sufficiently valid (**Table 2**).[20] Although RCTs represent a high level of evidence, the trial by Bishnu et al had poor validity due to its open-label design and high drop-out rates (**Table 2**).[21] The retrospective cohort study by Kaplan et al represents a lower level of evidence than the other studies but is valuable because of its large sample size and good internal validity (**Tables 2 and 3**).[22]

Table 3 shows generally favorable mortality outcomes with statin therapy in liver cirrhosis patients. The meta-analysis by Kim et al reported a 46% reduction in mortality with statin therapy based on a pooled analysis from one RCT and four retrospective cohort studies (pooled RR: 0.54, P<0.05).[20] This finding was supported by Kaplan et al, who reported significantly reduced mortality with a cumulative annual statin therapy (HR: 0.913, P<0.0001). They also reported that patients using statins at baseline had reduced mortality compared to patients who were never treated with statins (HR: 0.943, p<0.05).[22] In contrast, Bishnu et al reported no statistical difference in mortality between the intervention and control groups.[21] However, this study was an open-label proof-of-concept RCT with a primary

Table 3. Study designs and main findings.

Study	Study Population	Intervention and Control	Mortality Outcomes
Kim et al (Meta-Analysis)	Four retrospective cohort studies and one RCT included. Total number of patients in the mortality analysis: N = 8,017	Statin therapy (intervention) vs no statin therapy (control)	**Pooled relative risk for all-cause mortality**: 0.54 (95% CI: 0.47–0.61) with statin therapy in liver cirrhosis patients
Bishnu et al (RCT)	30 patients with evidence of portal hypertension were analyzed	Patients were randomized to receive 40 mg propanolol + 20 mg atorvastatin daily (intervention) or 40 mg propanolol only (control) for 30 days.	At a one-year follow-up, 1/12 patients died in the control group (8.33%) and 0/11 patients died in the intervention group. **(chi-square p=1.000)**
Kaplan et al (Retrospective Cohort Study)	A total of 74,984 patients were analyzed. There were 21,921 baseline statin users and 53,063 baseline statin naïve patients. Of the patients in the baseline statin naïve group, 8,794 patients received statin therapy during follow-up (statin initiators) and 44,269 never received statin therapy during follow-up (statin non-initiators).	Baseline statin users were compared with statin non-initiators Subgroup analysis: within statin naïve group, 6,481 statin initiators and 12,860 matched statin non-initiators were compared. The effect of cumulative statin therapy per-year on mortality was analyzed.	**Baseline statin users vs statin non-initiators:** HR: 0.943 (95% CI: 0.926–0.971, p<0.05) **Statin initiators vs statin non-initiators:** HR: 0.913 (95% CI: 0.890–0.936, p<0.0001) (with cumulative per-year statin therapy)

RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval.

outcome measure of HVPG reduction and not mortality. The initial sample size in each group was small (N=15) with a significant overall loss to follow-up (23.3%). No sample size or power calculation was conducted prior to the study. Hence, this RCT has a high risk of bias, and its results must be interpreted with caution.

A retrospective cohort study by Chang et al reported that within the statin group, a cumulative defined daily dose of 28 vs 28–365 vs > 365 had associated HRs of 1 vs 0.61 vs 0.24, respectively (overall P<0.0001).[23] This dose-dependent pattern strengthens the evidence for mortality benefits with statin therapy in liver cirrhosis patients. This study was included in the meta-analysis by Kim et al.[20]

Evidence suggests that the survival benefits of statins may be limited to Child-Pugh class A and B patients only. An RCT by Abraldes et al demonstrated that statin administration significantly reduced mortality in Child-Pugh class A and B patients (P=0.006) but not in Child-Pugh class C patients (P=0.295).[24] Similarly, Kaplan et al found that cumulative statin therapy significantly reduced mortality in Child-Pugh A (P<0.0001) and Child-Pugh B (P=0.0005) patients but not in Child-Pugh C patients (P=0.64).[22] This finding suggests that statins may be more beneficial in patients in early stages of cirrhosis. However, the number of Child-Pugh C patients in both studies was significantly fewer than that of Child-Pugh A and B patients (23 vs 124 in Abraldes et al and 130 vs 20,211 in Kaplan et al). Hence, this observation could be due to the small sample size of Child-Pugh C patients leading to insufficient power to reach statistical significance.

The main proposed mechanism for mortality reduction with statin therapy in liver cirrhosis patients is reduction of portal pressure. Statins achieve this by upregulating KLF-2, increasing expression and activation of eNOS, and increasing intrahepatic NO levels.[12–14,17] Portal hypertension is associated with the development and bleeding of gastroesophageal varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy.[25] Three RCTs have reported significantly reduced portal pressure with statin therapy compared to control groups.[15,16,21] A reduction in portal pressure is associated with a reduced risk of variceal bleeding, re-bleeding, and overall mortality.[8]

Statins could also reduce mortality by preventing serious infections, HCC, and hepatic decompensation.[26] The occurrence of infections in cirrhosis increases the risk of kidney injury, hepatic encephalopathy, and mortality. A large population-based study reported that statins were associated with a reduced incidence of hospital-associated infections (HR: 0.67; 95% CI: 0.47-0.95) through unknown mechanisms.[27] A meta-analysis reported that statins were associated with a reduced risk of progression to HCC in chronic hepatitis C patients (pooled RR: 0.45, P=0.021),[28] which is possibly due to their anti-neoplastic effects.[18] In addition, the meta-analysis by Kim et al demonstrated significantly reduced rates of hepatic decompensation with statin therapy in chronic liver disease and liver cirrhosis patients.[20]

The primary concern with statin administration in patients with liver disease is safety, since statins undergo first pass metabolism and can elevate liver enzymes.[26] However, studies have shown that statins are well-tolerated in patients with chronic liver disease.[29,30] Previous RCTs on patients with compensated liver cirrhosis reported no differences in adverse effects and liver enzyme elevation with or without statin administration.[15,16] Nevertheless, an RCT on decompensated cirrhosis patients reported an increased risk of rhabdomyolysis with simvastatin administration.[24] The National Lipid Association's Safety Task Force concluded that statins are not contraindicated in chronic liver disease or compensated cirrhosis but must be used with caution in decompensated cirrhosis patients.[31]

Statins are widely available at a relatively low cost. Moreover, the benefits of statins are suggested to be additive to NSBBs in cirrhosis.[32] If proven to be effective and safe, the addition of statins could be a feasible and cost-effective solution to decelerate the progression of cirrhosis. Cost-effectiveness is of additional importance in developing economies, such as Indonesia, which is currently in transition toward universal health coverage through its national insurance program,

Jaminan Kesehatan Nasional.

The main limitation of this evidence-based case report is the scarcity of high level evidence. Cohort studies, especially retrospective cohort studies, are prone to bias, and represent a lower level of evidence than RCTs and meta-analyses. Although meta-analyses represent the highest level of evidence, the study by Kim et al consisted of four retrospective cohort studies and one RCT. Hence, most of the current data on statins and mortality in cirrhosis patients comes from retrospective cohort studies, which are inferior to prospective cohort studies and RCTs. More high quality studies are required before statin administration can be widely recommended for cirrhosis patients in daily clinical practice.

CONCLUSION

The current evidence suggests that statin therapy is potentially beneficial in reducing mortality in liver cirrhosis patients. This benefit seems to be limited to Child-Pugh class A and B patients; however, this benefit must be confirmed in a larger cohort of Child-Pugh C patients. High quality prospective cohort studies and RCTs are required to confirm the survival benefits of statin therapy in cirrhosis patients before they can be widely recommended.

Our patient had advanced stage Child-Pugh class C cirrhosis with refractory ascites, which suggests decompensation. The current evidence suggests that the benefit and safety profile of statin therapy for decompensated liver cirrhosis is unfavorable. Hence, statin therapy was not recommended for this patient.

CONFLICTS OF INTEREST

The authors of this study state that they have no conflicts of interest.

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Predicting Parameters of Renal Function Recoverability After Obstructive Uropathy Treatment in Adults

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ABSTRACT

Obstructive uropathy can have many causes and can manifest as supravesical, vesical, or infravesical levels of obstruction. Treatment of obstructive uropathy, whether definitive or temporary, has a risk of complications or could worsen the patient's quality of life. Thus, knowledge of the parameters that predict recoverability of renal function after obstructive uropathy treatment is essential for patients and their families. Several studies have evaluated many factors that might potentially predict recoverability of renal function after obstruction release and these essentially are divided into factors predicting unilateral or bilateral obstruction. Almost all unilateral obstruction studies used ureteropelvic junction obstruction cases as their subjects and utilized nuclear scan renography to evaluate kidney recoverability. Factors confirmed as predicting factors for recoverability of renal function were age, hemoglobin level, BUN-to-creatinine ratio, postoperative urine volume and sodium excretion, cortical thickness, type of renal pelvis, hydronephrosis grade, corticomedullary differentiation, parenchymal echogenicity, renal resistive index, and initial kidney function. Thus, these studies all had different criteria for defining the recovery of renal function, and this might explain the differences observed from study to study.

Keywords**:** *Hydronephrosis, obstructive uropathy, predicting factor, recoverability, renal function.*

INTRODUCTION

Hydronephrosis is a term used to describe a dilated renal pelvis, with or without involvement of its calyces, and might arise due to a physiological or pathological condition.[1] In the physiological situation, a dilatation of a urinary tract structure can occur following events such as diuresis, increased intra-abdominal pressure (e.g., straining), or the influence of gravity.[2] This dilatation is essential to allow efficient urine expulsion from the renal pelvis.[2,3] However, in a pathological condition, also known as obstructive uropathy, a dilatation of the urinary tract structure happens in response to obstruction at the supravesical, vesical, or infravesical level.[4–7]

In women, obstructive uropathy can occur due to pelvic organ prolapse.[8–10] In men, hydronephrosis may follow a benign prostatic obstruction.[11] Regardless of gender, other common causes of obstructive uropathy include urinary tract stone disease, urothelial carcinoma, other malignancies, and neurogenic bladder.[4,5,12] To a lesser degree, obstructive uropathy can also be induced by infection, drug administration, and radiotherapy.[13–15] Therefore, complaints related to obstructive uropathy may vary depending on the underlying cause.[16] The presence of obstructive uropathy is also crucial in determining the prognosis and disease progression.[17–19]

If obstructive uropathy is not suitably treated, it may cause irreversible structural changes and deteriorate renal function.[20,21] Irrespective of the cause of the obstruction, optimal urine diversion is a mainstay in addition to definitive treatment and is performed using an indwelling catheter, double-J stent (DJ stent), or nephrostomy tube according to the obstruction location. However, the use of a urine diversion method, and specifically the DJ stent insertion and the nephrostomy tube, often harms the patient's quality of life (QoL).[22] Moreover, urine diversion does not provide a complete guarantee of return of full renal function after definitive treatment. This could be due to the occurrence of other pathological processes that affect kidney function in addition to obstructive uropathy. The duration of urinary tract obstruction is mostly unknown, especially in silent ureteral stone disease or malignancy.[20,23]

The risk of complications associated with definitive treatment or urinary diversion, as well as the possibility of worsening the patient's QOL by urinary diversion, necessitate thorough discussion with the patient and family, especially regarding disease prognosis. Therefore, knowledge of the parameters that could predict renal function recoverability after obstructive uropathy treatment is essential. The aim of this review is to explore those parameters based on the currently available literature.

EFFECTS OF OBSTRUCTIVE UROPATHY ON THE KIDNEY

Acute kidney injury (AKI), or even chronic kidney disease, can occur due to obstructive uropathy, especially with bilateral obstruction.[24] The obstruction effects on the kidney can be influenced by factors such as the duration, extent (partial or complete obstruction), or position (unilateral or bilateral obstruction) of the obstruction, as well as infection and the initial renal function.[25,26] The difference between unilateral ureteral obstruction (UUO) and bilateral ureteral obstruction (BUO) lies in the ureteral pressure and renal blood flow within the acute phase. The total glomerular filtration rate (GFR) is still maintained in UUO and prevents acute kidney injury due to the presence of a functional contralateral kidney; nevertheless, the affected kidney will suffer GFR decrease and tubular damage within five minutes after the onset of the obstruction.[24,27,28] Tubular damage causes kidney tubular dysfunction. Dysfunction of ion transport and urinary acidification is seen in both UUO and BUO. However, the urine concentrating ability due to Aquaporin-2 impairment is more marked in BUO, whereas hypertrophy of the contralateral kidney is seen for compensation in UUO.[27]

Damage from interstitial fibrosis becomes significant following renal obstruction.[24,27,28] Inflammatory cells, such as leukocytes and macrophages, infiltrate in the early stage of obstruction, and they produce several cytokines. Cytokines and vasoactive agents, like Tumor Necrosis Factor α (TNF-α), Transforming Growth Factor β (TGF-β), Angiotensin II, and Interleukin-18, are believed responsible for the occurrence of interstitial fibrosis.[27,29,30] Apoptosis also occurs due to obstructive uropathy and leads to tubular and interstitial atrophy.[29] An animal study has also indicated that fibrosis progression continues even after release of the obstruction.[26]

Microscopically, the apoptosis of tubular and interstitial cells begins as soon as four days after onset of the obstruction and peaks at day 15. Thinning of the kidney parenchymal tissue can be seen within a month. Most experts agree that a kidney obstruction lasting longer than six weeks causes irreversible damage.[27,28] Therefore, any delay in obstruction release can affect long-term renal function.[31]

PERIOPERATIVE PARAMETERS PREDICTING KIDNEY FUNCTION RECOVERABILITY AFTER OBSTRUCTION RELEASE

A summary of the current literature discussing the predicting parameters of recoverability kidney function after obstructive uropathy release in unilateral obstruction is shown in **Table 1**. A similar summary for bilateral obstruction or unilateral obstruction in single kidney patient is shown in **Table 2**. A summary of parameters that are positively correlated with kidney function recoverability after obstruction release is shown in **Figure 1.**

Table 1. Predicting parameters of renal function recoverability after obstructive treatment in unilateral obstruction

Author and year of study	Type of Study and Analysis	Population and Obstructive Treatment	Parameters Studied	Recovery Renal Function Criteria	Results/Conclusion
Harraz et al. (2014)[32]	Retrospective; multivariate analysis	Unilateral UPJO with normal contralateral kidney; Anderson-Hynes dismembered pyeloplasty	- Age - Sex - PO DRF - PO ipsilateral GFR - Cortical thickness - Renal pelvis antero-posterior diameter	Not specified	Lower baseline DRF (<40%) and thicker cortical thickness were predicting parameters for renal function improvement
Liu et al. (2015)[33]	Retrospective; bivariate analysis	Unilateral UPJO with normal contralateral kidney; Anderson-Hynes dismembered pyeloplasty	- PO TTT - PO DRF - Side of affected kidney - Surgery method	> 5% DRF increase compared to basal value using 99mTC-DTPA	PO delayed TTT positively associated with renal function improvement
Li et al. (2018)[34]	Retrospective; multivariate analysis	Unilateral UPJO and normal contralateral kidney; Anderson-Hynes dismembered pyeloplasty	- Age - Gender - BMI - Comorbidity (diabetes, hypertension) - Health-related behavior (alcohol, tobacco) - PO symptom - Affected side - Renal pelvic type (intraparenchymal or extraparenchymal) - Length of narrow segment - Hydronephrosis grade - PHAR - PO renal RI - POR renal RI declined - PO DRF - POR DRF	>10% DRF improvement in affected kidney using 99mTC-MAG3 diuretic renography	Parameters affecting recoverability of renal function, based on bivariate analysis: - Age - History of hypertension - Renal pelvic type - Hydronephrosis grade - PHAR - PO renal RI - 3-, 6-, and 12-month POR renal RI decline - PO DRF Parameters affecting recoverability of renal function in patients < 35 years old, based on multivariate analysis: - Renal pelvic type - Hydronephrosis grade

BMI, body mass index; BCR, BUN-to-creatinine ratio; BUN, blood urea nitrogen; CMD, corticomedullary differentiation; CrCl, creatinine clearance; DRF, differential renal function; GFR: glomerular filtration rate; IPP, intrapelvic pressure; PCN, percutaneous nephrostomy; PHAR, renal parenchyma to hydronephrosis area ratio; PO, preoperative; POR, postoperative; RI, resistive index; TTT, tissue tracer transit; UPJO, ureteropelvic junction obstruction; USG; ultrasonography

Table 1. Predicting parameters of renal function recoverability after obstructive treatment in unilateral obstruction (cont.)

Author and year of study	Type of Study and Analysis	Population and Obstructive Treatment	Parameter Studied	Recovery Renal Function Criteria	Results / Conclusion
					- PHAR - PO renal RI - 12-month POR renal RI decline Parameters affecting recoverability of renal function in patients > 35 years old, based on multivariate analysis: - Renal pelvic type - Hydronephrosis grade - PHAR
Khalaf et al. (2004)[35]	Prospective; multivariate analysis	Unilateral obstructive uropathy with normal contralateral kidney; various treatment	- Parenchymal thickness - Reduction in length of the ipsilateral kidney after treatment - Reduction in width of the ipsilateral kidney after treatment - Parenchymal echogenicity - CMD - Compensatory hypertrophy of the contralateral kidney - PO ipsilateral kidney GFR - Renal perfusion of the ipsilateral kidney (using 99mTC-DTPA) - PO renal RI of the ipsilateral kidney - Changes in the RI of the ipsilateral kidney after treatment	> 5% GFR increase compared to basal value using 99mTC-DTPA	Parameters affecting recoverability of renal function, based on bivariate analysis: - PO ipsilateral kidney GFR - Renal perfusion of ipsilateral kidney - Parenchymal thickness - Parenchymal echogenicity - Corticomedullary differentiation - Changes of RI of ipsilateral kidney after treatment - Compensatory hypertrophy of contralateral kidney Parameters affecting recoverability of renal function, based on multivariate analysis: - Renal perfusion of ipsilateral kidney - PO ipsilateral kidney GFR

BMI, body mass index; BCR, BUN-to-creatinine ratio; BUN, blood urea nitrogen; CMD, corticomedullary differentiation; CrCl, creatinine clearance; DRF, differential renal function; GFR: glomerular filtration rate; IPP, intrapelvic pressure; PCN, percutaneous nephrostomy; PHAR, renal parenchyma to hydronephrosis area ratio; PO, preoperative; POR, postoperative; RI, resistive index; TTT, tissue tracer transit; UPJO, ureteropelvic junction obstruction; USG; ultrasonography

Table 1. Predicting parameters of renal function recoverability after obstructive treatment in unilateral obstruction (cont.)

Author and year of study	Type of Study and Analysis	Population and Obstructive Treatment	Parameter Studied	Recovery Renal Function Criteria	Results / Conclusion
					PO GFR value > 10 ml/min/1.73 m^2 could predict stabilization or improvement of renal function after obstruction release
Ortapamuk et al. (2003)[36]	Prospective; bivariate analysis	Unilateral UPJO with normal contralateral kidney; Anderson-Hynes dismembered pyeloplasty	- Age - Symptom (infection, pain) - PO DRF Parenchymal thickness	>5% DRF improvement in affected kidney using 99mTC-MAG3 diuretic renography, 6 months after surgery	No factor could predict recovery of renal function after obstruction release
Wu et al. (2012)[37]	Retrospective; multivariate analysis	Unilateral > 6 months obstructive uropathy with various causes; various treatment	- Age - Comorbidity (diabetes, hypertension) - Health-related behavior (alcohol, tobacco, drug use) - PO DRF	>7% DRF improvement in affected kidney using 99mTC-MAG3 diuretic renography	Younger age and lower PO DRF could predict > 7% DRF improvement

BMI, body mass index; BCR, BUN-to-creatinine ratio; BUN, blood urea nitrogen; CMD, corticomedullary differentiation; CrCl, creatinine clearance; DRF, differential renal function; GFR: glomerular filtration rate; IPP, intrapelvic pressure; PCN, percutaneous nephrostomy; PHAR, renal parenchyma to hydronephrosis area ratio; PO, preoperative; POR, postoperative; RI, resistive index; TTT, tissue tracer transit; UPJO, ureteropelvic junction obstruction; USG; ultrasonography

Table 2. Predicting parameters of renal function recoverability after obstructive treatment in bilateral obstruction or unilateral obstruction in a single kidney

Author and year of study	Type of Study and Analysis	Population and Obstructive Treatment	Parameter Studied	Recovery Renal Function Criteria	Results/Conclusion
Bundu et al. (2018)[38]	Retrospective; bivariate analysis	Obstructive uropathy patients; treatment not specified	- Obstructive etiology - PO hemoglobin level - PO blood glucose level - PO serum potassium level - PO BCR - Parenchymal thickness	Serum creatinine < 2 mg/dL, 2 months after obstruction release	Parenchymal thickness ≥ 10 mm, hemoglobin ≥ 10 mg/dL, and BCR ≥ 10 positively associated with renal function recoverability
Hussain et al. (1997)[39]	Prospective; bivariate analysis	Obstructive uropathy due to stone disease; PCN	- Kidney size - Degree of hydronephrosis - Cortical thickness - POR urine volume - POR urine pH - POR urinary sodium	Serum creatinine < 3 mg/ dL or CrCl > 10 ml/ minute, 3 months after obstruction release	POR urine pH < 6, 2-8 L/24 hours POR diuresis, and POR urinary sodium > 30 mEq/L positively associated with renal function recoverability
Lutaif et al. (2003)[40]	Prospective; bivariate analysis	Obstructive uropathy due to stage III-IV cervical cancer; PCN	- Age - Need for dialysis before PCN - History of radiotherapy treatment - Degree of hydronephrosis - Cortical thickness	Serum creatinine < 1.4 mg/ dL, 1 month after obstruction release	Younger age and cortical thickness positively associated with renal function recoverability
Shokeir et al. (2002)[41]	Prospective; bivariate analysis	Obstructive uropathy with anuria; various treatments	- 3-day POR renal RI difference	>20% reduction of serum creatinine value, 3 days after obstruction release	Reduction POR renal RI could predict recovery of renal function after obstruction release Mean difference of renal RI change for good recovery of renal function was 0.14

BMI, body mass index; BCR, BUN-to-creatinine ratio; BUN, blood urea nitrogen; CMD, corticomedullary differentiation; CrCl, creatinine clearance; DRF, differential renal function; GFR: glomerular filtration rate; IPP, intrapelvic pressure; PCN, percutaneous nephrostomy; PHAR, renal parenchyma to hydronephrosis area ratio; PO, preoperative; POR, postoperative; RI, resistive index; TTT, tissue tracer transit; UPJO, ureteropelvic junction obstruction; USG; ultrasonography

Table 2. Predicting parameters of renal function recoverability after obstructive treatment in bilateral obstruction or unilateral obstruction in a single kidney (cont.)

Author and year of study	Type of Study and Analysis	Population and Obstructive Treatment	Parameter Studied	Recovery Renal Function Criteria	Results / Conclusion
Sharma et al (2015)[42]	Prospective; multivariate analysis	Moderate-severe hydronephrosis due to chronic complete ureteral obstruction and had chronic renal failure; PCN	- Infection presentation - PO serum creatinine level - POR Urine pH - Renal length and width - Cortical thickness - Hydronephrosis grade - IPP - PCN output - CMD - Parenchymal echogenicity - Contralateral kidney status	>10% CrCl improvement compared to basal value at 1 month after obstruction release	Parameters affecting recoverability of renal function, based on bivariate analysis: - IPP - PCN output - PO serum creatinine level - Urine pH - Parenchymal echogenicity - Hydronephrosis grade - CMD - Contralateral kidney status Parameters affecting recoverability of renal function, based on multivariate analysis: - CMD - Parenchymal echogenicity - PO serum creatinine level - Contralateral kidney status

BMI, body mass index; BCR, BUN-to-creatinine ratio; BUN, blood urea nitrogen; CMD, corticomedullary differentiation; CrCl, creatinine clearance; DRF, differential renal function; GFR: glomerular filtration rate; IPP, intrapelvic pressure; PCN, percutaneous nephrostomy; PHAR, renal parenchyma to hydronephrosis area ratio; PO, preoperative; POR, postoperative; RI, resistive index; TTT, tissue tracer transit; UPJO, ureteropelvic junction obstruction; USG; ultrasonography

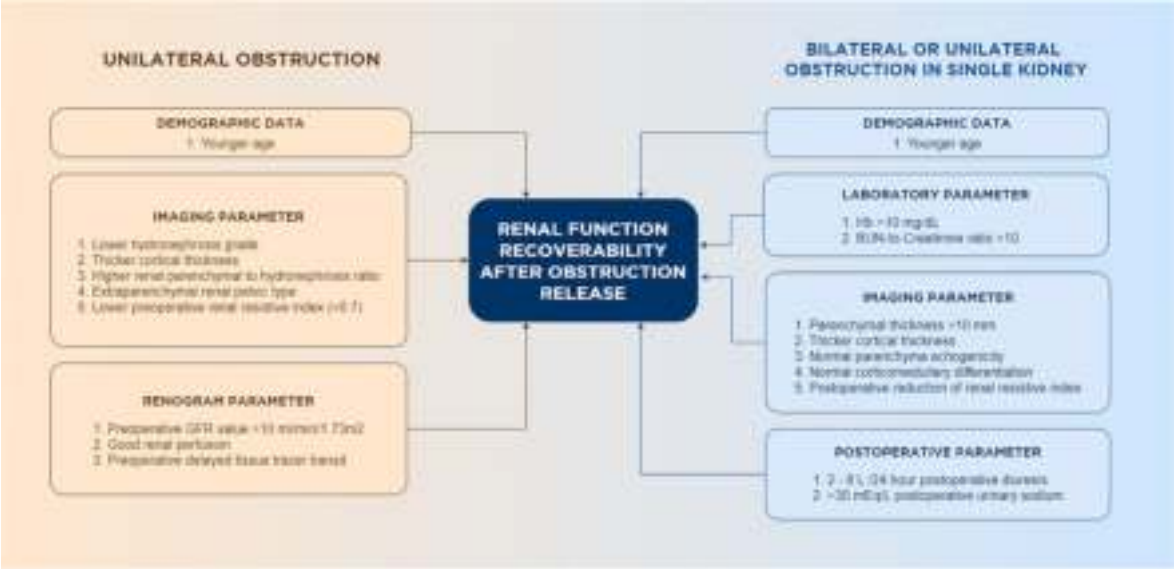

Figure 1.

Patient History and Demographic Characteristics

Patient history and demographic characteristics, such as age, sex, history of diabetes and hypertension, health-related behavior (smoking, alcohol drinking, or drug use), obstruction-related symptoms, and obstruction etiology, have been discussed in the current literature studying the recoverability of kidney function after obstruction release. Age is known to have negative effects on structural and functional kidney changes. The development of nephrosclerosis and a decrease in nephron number leads to a reduction in the glomerular filtration rate (GFR).[43] Hypertension and diabetes mellitus are other known independent risk factors for kidney disease and are more commonly seen in older patients.[44,45] Conflicting results have been reported regarding the association between smoking and alcohol drinking and kidney disease. Theoretically, smoking could lead to kidney damage and early studies showed that smoking or drinking more than four serving of alcohol per day was associated with chronic kidney disease (CKD). However, the current literature does not identify these as independent risk factors for CKD. Drug use, such as heroin or cocaine use, has a confirmed association with CKD.[46,47] Gender can also influence the occurrence of kidney disease, with a more rapid decline in kidney function seen in men than in women due to a protective effect of estrogen.[48] No evidence currently suggests that obstruction-related symptoms, such as pain, are signs of persisting renal function, and no difference in renal recovery is observed between benign and malignant causes after obstruction treatment.[49]

Of the factors studied, age was the only parameter that could predict recoverability of renal function after obstruction release according to three studies, and younger age was positively correlated with recoverability.[34,37,40] One study used a cut-off value of 35 years of age in predicting recoverability of renal function.[34]

Lab Parameters

The levels of blood glucose, serum potassium, and hemoglobin, the BUN-to-creatinine ratio (BCR), the urine pH, and the postoperative urinary sodium levels have been evaluated for their possible roles in predicting kidney function recoverability. Only the hemoglobin level, BCR, urine pH, and postoperative urinary sodium levels were predictive parameters. [38,39]

Hemoglobin can be affected by several factors, such as bleeding or nutritional status. However, in a kidney that develops CKD, anemia becomes one of the signs due to depletion of the erythropoietin level.[50] A hemoglobin level > 10 mg/dL has a positive association with the return of kidney function after obstruction release.[38]

A direct relationship between urine pH and acute or chronic kidney failure is not clear. Low urine pH is associated with metabolic syndrome, which is a risk factor of CKD, and metabolic acidosis is also a common feature in CKD.[51,52] Low urinary pH has also been viewed as a predictor of CKD, and alkaline urine could be a protective factor for decreased renal function.[53,54] On the contrary, Hussain et al. showed that a urine pH < 6 had a positive association with the recoverability of renal function. This urine pH sample was taken from a nephrostomy tube following administration of an antibiotic to prevent the influence of urea-splitting organisms on urine pH.[39] This contradictory result is still unresolved.

Historically, the BCR has been used to differentiate between pre-renal and intra-renal causes of AKI, with a ratio of 10:1 considered normal and a ratio greater than 20:1 considered a pre-renal cause of AKI.[55,56] Increased BCR in prerenal AKI occurs due to elevation of the antidiuretic hormone (ADH) levels, leading to increased urea reabsorption. However, this cut-off value for the BCR is currently in question.[56,57] In a uropathy obstructive state, an elevation of BCR is expected due to the slower blood flow through the vasa recta. The slower urinary flow due to the obstruction also causes an increase in the urea reabsorption time, thereby leading to a higher total urea reabsorption.[55] A BCR of more than 10:1 is a predicting factor of renal recovery after obstruction release, even though the theoretical explanation underlying this cut-off value is unclear.[38] Therefore, the exact cut-off value for BCR in predicting renal recoverability after obstruction release should be studied further. The elevation in BCR could also be caused by many other factors that increase urea production, such as a high protein diet and gastrointestinal bleeding.[57] Thus, caution is needed when using this parameter.

Natriuresis of more than 30 mEq/L is associated with the recovery potential of kidney function.[39] It is correlated with post obstructive diuresis (POD), which will be further discussed in the subsection on postoperative clinical parameters.

Imaging

Kidney Anatomy Evaluation

The following kidney anatomy parameters have been studied for their roles in predicting kidney function return after obstruction release: kidney size, cortical and parenchymal thickness, parenchymal echogenicity, corticomedullary differentiation (CMD), degree of hydronephrosis, renal parenchyma to hydronephrosis ratio (PHAR), and type of renal pelvis (either intra-parenchymal or extra-parenchymal).

Kidney size, cortical and parenchymal thickness, and CMD can be evaluated using ultrasonography (USG). The normal values for renal length, cortical thickness, and parenchymal thickness are 10–12 cm, 7–10 mm, and 15–20 mm, respectively. Cortical thinning is a sign that can be radiographically observed in patients with hydronephrosis.[58] A reduction in cortical thickness may reflect atrophy as part of the pathogenesis of hydronephrosis.[12] When the cortex and medulla are difficult to differentiate, which is defined as poor CMD, the parenchymal thickness can be used instead of the cortical thickness.[58] Thicker parenchymal and cortical thicknesses are associated with better potential of recoverability of kidney function, with no return of kidney function observed when the cortical thickness is less than 12 mm.[38,40] CMD can also predict the return of kidney function, according to multivariate analysis.[42] Recent studies have failed to show kidney size as a predicting factor for return of kidney function.[39,42]

Parenchymal echogenicity can also be evaluated using USG. Renal parenchyma echogenicity is determined by comparing it with that of the liver or spleen parenchyma, which is usually isoechoic or hyperechoic.[59] Increased renal echogenicity could indicate fibrosis or severe interstitial infiltration and tubular atrophy.[60] A multivariate analysis by Sharma et al. showed that parenchymal echogenicity had a significant relationship with renal function recoverability after obstruction release.[42] It was also correlated with decreased eGFR, while decreased eGFR indicated a poor prognosis for renal function recoverability.[60]

A study conducted by Li et al. demonstrated that the degree of hydronephrosis and PHAR could predict the return of kidney function after obstruction release, irrespective of the patient's age.[34] The degree of hydronephrosis and PHAR can be evaluated using several methods other than USG, such as computed tomography (CT) scans, magnetic resonance imaging (MRI), or intravenous pyelography (IVP). Li et al. used USG to determine the SFU classification for the degree of hydronephrosis and PHAR was calculated using a contrast CT scan.[34] In infants, PHAR is a promising parameter for predicting surgery success in patients with high-grade prenatal hydronephrosis.[61]

The renal pelvic type is considered extraparenchymal if more than 50% of the renal pelvis is contained outside the kidney parenchymal volume, and intraparenchymal if more than 50% of the renal pelvis is contained inside the kidney parenchymal volume. The extraparenchymal type of pelvis is positively correlated with kidney function improvement after obstruction treatment.[34] This might reflect the small volume that is constrained in the intraparenchymal pelvis, so a volume excess could lead to high intrapelvic pressure.[62] Thus, hypothetically, less compliance is found in the intraparenchymal renal pelvis, making it more susceptible to obstruction. However, this theory requires further proof.

Kidney function evaluation

The kidney function evaluation parameters of renal perfusion, differential renal function (DRF), and tissue tracer transit (TTT) were used to predict recoverability of kidney function were studied in adult ureteropelvic junction obstruction (UPJO) patients. These three parameters were obtained using nuclear scan renography, either 99mTC-MAG3 or 99mTC-DTPA, and were confirmed in current studies as potential parameters for predicting recovery of renal function.[33-35,37]

Khalaf et al. found that good renal perfusion was positively correlated with the recoverability of renal function. Renal perfusion is determined using 99mTC-DTPA and is considered good perfusion if the first 30 seconds of the vascular phase after tracer injection represents one third or more of the total curve counts.[35]

Better recoverability of renal function was found for a low DRF than for a higher one.[32,37] However, this finding was challenged by Li et al., who found a higher baseline DRF in a group showing kidney function improvement after treatment.[34] Moreover, a kidney with a DRF less than 10% has long been known to have a small chance of recovery.[25]

The TTT is defined as the transit of a physiological tracer from the parenchyma to the renal pelvis and is considered delayed if the tracer transit is slower than that in the contralateral kidney. A tracer that is relatively stable within the kidney in images at three and nine minutes or a tracer that shows increased activity in the renal parenchymal is a sign of delayed TTT. Liu et al. showed that delayed TTT was positively associated with the return of kidney function after therapy.[33]

Resistive index (RI) measurement

RI is measured using Doppler USG. Renal RI can be calculated as the peak systolic velocity – end diastolic velocity divided by peak systolic velocity when the Doppler USG image is obtained on the interlobar renal artery.[63] A high renal RI (> 0.65) was associated with severe renal fibrosis and a decrease in renal function.[64] This result agrees with that of Li et al., who showed a correlation between a lower preoperative RI and better recoverability of kidney function.[34] A study by Shokeir et al. also reported that a mean difference between postoperative and preoperative RI of 0.14 indicated a good chance of renal function return.[35]

Intraoperative Parameter

Intrapelvic pressure can be measured intraoperatively during percutaneous nephrostomy (PCN). This parameter was measured using a manometer after putting a needle inside the kidney with the mid-axillary line as its reference point.[42] Even though this pressure showed significant correlation with recoverability of renal function after obstruction release, it failed to show a significant influence in multivariate analysis.[42]

Postoperative Clinical Parameters

Postoperative diuresis of 2–8 liters per 24 h after obstruction release is associated with better outcomes in terms of renal recovery.[39] Decompression of a renal obstruction leads to post-obstructive diuresis (POD), which is a physiological response when body tries to eliminate excess water and solutes due to an obstruction. POD usually happens in patients with bilateral obstruction or a single-kidney unilateral obstruction.[65] This physiological polyuria response lasts for less than 48 h, and if it persists more than 48 h, pathological POD occurs. Therefore, as it is a natural response, POD might be a good sign for kidney function return. However, careful monitoring should be done due to the risk of dehydration and electrolyte imbalance.[27]

FUTURE DIRECTIONS

The literature available to date indicate that different criteria are used to determine the recoverability of renal function after obstruction release. Nuclear scan renography has been used in unilateral obstruction, mostly due to UPJO, whereas laboratory parameters, such as GFR or serum creatinine, have been used in cases of bilateral obstruction or non-UPJO causes to assess kidney function. These differences cannot be circumvented due to the different natural courses of the disease between UUO and BUO. However, similar criteria should be used to evaluate the recoverability of renal function. This study proposes that an improvement of > 7% DRF and GFR > 30 ml/min/1.73 m^2 (Kidney Disease Outcomes Quality Initiative – KDOQI criteria) should be used as criteria for recoverability of renal function for unilateral and bilateral obstructions, respectively. A GFR > 30 ml/min/1.73 m^2 is proposed because the symptoms of CKD are commonly found in stage 4 and 5 disease.

CONCLUSION

Various perioperative parameters can predict the recoverability of renal function, but these vary from study to study. These differences might reflect the differences in the study populations and the criteria used to determine renal recoverability.

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