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Challenges in Diagnosis and Treatment of Male Hypogonadism

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Hypogonadism is a condition characterized by diminished or absent production of sex hormones by the testicles in men and the ovaries in women.[1] Hypogonadism is classified into primary and secondary hypogonadism. Each type of hypogonadism can be caused by congenital and acquired factors. There are many factors that contribute to the occurrence of hypogonadism, including genetic and developmental disorders, infection, kidney disease, liver disease, autoimmune disorders, chemotherapy, radiation, surgery, and trauma.[2,3] This represents the considerable challenge in diagnosing hypogonadism.

The diagnosis of hypogonadism in males is established based on medical history, physical examination, and gonadal hormone levels in the blood. The onset, disease duration, severity level, presence of comorbid conditions, and history of previous hormone therapy affect the diversity of sign and symptoms of hypogonadism. The signs and symptoms that present in pre-puberty will be different from those appearing post-puberty.[2] The variety of hypogonadism's causes and symptoms pose a significant challenge for healthcare providers in identifying this condition among those at risk and deciding whether treatment is necessary.

Diagnostic tests recommended for hypogonadism are testosterone measurements (total or free testosterone), ideally taken in the morning for two consecutive days; gonadotropins (FSH and LH or GnRH), to distinguish between primary or secondary hypogonadism if testosterone levels are low; dynamic tests; prolactin levels; and semen analysis to evaluate patient fertility; a fructose test if azoospermia is present. Dynamic test such as the GnRH stimulation test, clomiphene stimulation test, and hCG stimulation test are valuable for assessing hypothalamic and pituitary response. Additional examinations to determine the cause, comorbidities, location of abnormality, and complications may include bone density scans, pituitary MRI, buccal smears, testicular biopsy and scrotal exploration, and testicular ultrasound.[4]

The goals of treatment include restore sexual functionality and well-being, initiating and sustaining virilization, osteoporosis prevention, normalize growth hormone levels in elderly men if possible, and restoring fertility in instances of hypogonadotropic hypogonadism. The main approach to treating hypogonadism is hormone replacement therapy. Male with prostate cancer, breast cancer, and untreated prolactinoma are contraindicated for hormone replacement therapy.[4,5] When selecting a type of testosterone therapy for male with hypogonadism, several factors need to be considered, such as the diversity of treatment response and the type of testosterone formulation. The duration of therapy depends on individual response, therapeutic goals, signs and symptoms, and hormonal levels.[6] The response to testosterone therapy is evaluated based on symptoms and signs as well as improvements in hormone profiles in the blood. Endocrine Society Clinical Practice

Guideline recommend therapeutic goals based on the alleviation of symptoms and signs, as well as reaching testosterone levels between 400 – 700 ng/dL (one week after administering testosterone enanthate or cypionate) and maintaining baseline hematocrit.[7] Given the diversity of signs and symptoms, which may not always align with hormone levels in the blood, determining therapeutics goals can be challenging. Testosterone therapy may induced the changes of lipid profile, increase platelet aggregation and thrombogenicity, and also increase cardiovascular mortality.[4,8] To prevent the side effects of prolonged hormone use, regular assessments every 3 – 12 months are advised.[6]

Hormone therapy is the primary modality in the management of hypogonadism. The variety of signs and symptoms makes early diagnosis of this condition challenging. Moreover, administering hypogonadism therapy involves numerous considerations influenced by various patient factors and the potential for adverse effects. This poses a challenge for physicians to provide targeted hypogonadism therapy with minimal complications.

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Effectiveness and Safety of Nebulized Magnesium as Last Line Treatment in Adults with Acute Asthma Attack: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Asthma is a disease characterized by chronic airway inflammation, however one-third of asthmatic cases did not respond adequately. Inhaled magnesium has been proposed as a treatment for unresponsive asthma cases. However, its role remains controversial. This review evaluates the effectiveness and safety of nebulized magnesium compared to standard therapy (Beta Agonist, Anticholinergic, Corticosteroid) in adults with acute asthma attacks.* ***Methods:*** *The protocol has been registered in PROSPERO. A literature search was conducted through PubMed/MEDLINE, Cochrane, ProQuest, and Google Scholar, and using the keywords "inhaled magnesium" and "asthma". Manual searches were carried out through data portals. Journal articles included are randomized controlled trials. The assessment risk of bias was performed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.* ***Results:*** *There are five articles included in this review. There is no significant difference in readmission rate and oxygen saturation in the magnesium group compared to control (RR 1; 95% CI 0.92 to 1,08; p= 0,96 and MD 1,82; 95% CI -0.89 to 4.53; p= 0.19, respectively). There is a significant reduction of respiratory rate and clinical severity in magnesium (MD -1,72; 95% CI -3,1 to 0.35; p= 0.01, RR 0.29; 95% CI 0.17 to 0.69; p <0.001, respectively). There was a higher risk of side effects in the magnesium group (HR 1.56; 95%CI 1.05 to 2.32; p= 0.03). However, the side effects are relatively mild such as hypotension and nausea.* ***Conclusion:*** *Inhaled magnesium improves the outcome of asthmatic patients, especially in lung function, clinical severity, and respiratory rate. Moreover, inhaled magnesium is safe to be given.*

Keywords: *Inhaled Magnesium, Asthma, Adult.*

INTRODUCTION

Asthma is a disease characterized by chronic airway inflammation.[1] Manifestation of the disease includes shortness of breath, wheezing, and tightness in the chest. The symptom of the disease varies in terms of intensity and length. At first, the airflow in the respiratory tract is temporarily obstructed in the acute phase and it becomes irreversible in a later phase. Asthma is related to hyperreactivity of airway disease and inflammation.[2] In 2019, the World Health Organization (WHO) estimated 262 million people had asthma and asthma caused 455.000 deaths annually.[3] Asthma can be found in many countries all over the world, especially in low to middle-income countries. According to Indonesian Basic National Health Research in 2013, the prevalence of asthma reached 4.5%, specifically in Jakarta, the prevalence of asthma was 5.3%. [4] Based on the Global Initiative for Asthma (GINA), the standard treatment of asthma includes short-acting beta-agonists, corticosteroids, and anticholinergics.[4] However, there is 30% of patients unresponsive with these standard treatments.[5]

Magnesium is the fourth largest mineral in the human body. It is involved in 300 enzymatic reactions, especially in the metabolism of Adenosine Triphosphate (ATP). Magnesium is useful for muscle contraction, blood pressure, insulin regulation, and neural transmission. An imbalance of magnesium in the blood may induce abnormality in the neuromuscular and cardiology system.[6,7]

In recent years, magnesium has been studied as an additional medication for asthma. A report from Song et al showed that hypomagnesemia may worsen the severity of asthma.[8-10] Magnesium has an important role in the contraction and relaxation of airway muscle as it has a bronchodilation effect, inhibition of cholinergic, influx of calcium into the cell, and prevents histamine release.[11-14] The usage of magnesium for asthma nowadays is still limited by the intravenous route because it has numerous side effects such as palpitation, flushing, and hypotension. Therefore, nebulized magnesium has been proposed as the preferred route as it has fewer side effects.[9.10]

In previous studies, inhaled magnesium has shown various results. For example, Knightly et al showed that magnesium has a modest beneficial effect on pediatric and adult asthmatic patients. A systematic review published by Su et al concluded that inhaled magnesium had no effect in pediatric population.[15] Therefore, a systematic review of inhaled magnesium for adult asthmatic patients is considered necessary.

METHODS

This systematic review design is based on the 2009 PRISMA guidelines and has been registered in PROSPERO with the number Registration CRD42022362345. A literature search with PICO as follow: Population: Patient with asthma attack, above 18 years old; Intervention: Inhaled Magnesium +SABA+ Anticholinergic+ Corticosteroid; Comparation: SABA+ Corticosteroid+Anticholinergic; Outcome: Clinical Severity, Readmision, Lung Function, Vital Sign, Side Effect was conducted utilising databases namely PubMed/ Medline, Google Scholar, ProQuest, and Cochrane. The keywords of this literature search are "magnesium inhalation" or "magnesium nebulization" or "magnesium inhaled" or "magnesium nebulized" or "mgs04 inhaled" or "mgs04 nebulized" or "mgs04 inhalation" or "mgs04 nebulization" or "magnesium nebules" or "magnesium vaporized" AND "asthma" or asthma attack" or "asthma acute" or "acute asthma" or " asthma exacerbated" in English and Indonesian. Manual searching was conducted in national journal databases and libraries of medical faculty. We included randomized controlled trials comparing inhaled magnesium to standard therapy during asthma attacks in adult patients.

All journals were selected that met the inclusion criteria such as a randomized controlled trial, the sample of population being adult asthmatic patients above 18 years old, a study that compared inhaled magnesium and standard therapy, no limitation in language, and no limitation in a year of publication. The study was excluded such as literature review, and commentary.

Data extracted from each study that met the eligibility criteria included the basic

characteristics of the study, the characteristics of the study population, and the outcomes presented in a descriptive table. The basic characteristics of the study include the name of the main investigator, year of publication, study design, assessment of the asthmatic attack, and duration of the study. The characteristics of the study population consisted of the number of samples, age, sex, disease stage, lung function, and readmission rate. Outcomes collected from the study were readmission rate, clinical severity, mean difference in vital signs, and lung function. The primary outcome is clinical severity, vital signs, lung function, and readmission rate. The secondary outcome is the side effect.

The risk of bias assessment was performed by two independent investigators using Version 2 of the Cochrane risk-of-bias tool (RoB2) for randomized trials. Any conflicting decision would be resolved by consensus with a third investigator. Statistical analysis of this systematic review was conducted using RevMan 5.4 software (*Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen*). Heterogeneity was analyzed by I^2 test with grading low (0-25), moderate (26-50), substantial (50-75), and significant (>75%). If the analysis shows low and moderate heterogeneity, investigators chose a random effect model. However, if the analysis shows significant heterogeneity, investigators chose a fixed effect model. Investigators did not analyze the publication bias because the amount of articles is less than ten.

RESULTS

Based on the systematic search in four databases, 953 records were collected (**Figure 1**).

Duplications were removed and after a thorough reading of the abstract and title, we excluded 936 studies. Finally, five RCTs were included in this systematic review. The articles were from Ahuja et al, Goodcare et al, Gallegos et al, Hossein et al, and Motamed et al.[16-20]

The reviewer analyzed the risk of bias by using five parameters, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome measurement, and incomplete outcome data. In the random sequence generation aspect, Ahuja et al have an unclear risk of bias because this article does not mention the randomization method.[17] The study conducted by Goodacre, et al, had a low risk of bias because they used block

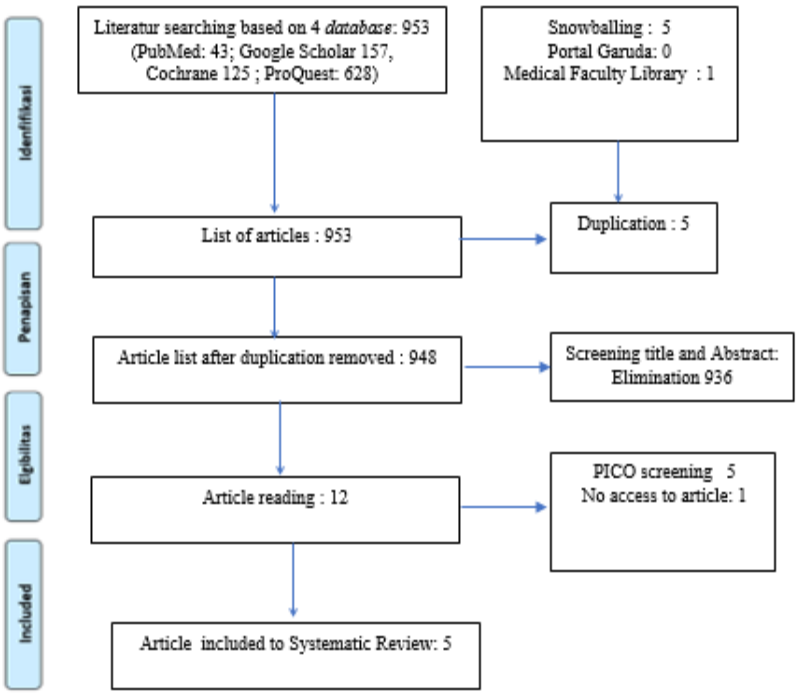

Figure 1. PRISMA chart.

randomization.[19] Study conducted by Motamed, et al, also had a low risk of bias because they used the block method.[20] Hossein et al used computer-generated software.[18] Study from Gallegos et al has a low risk of bias because they randomized the patient on arrival.[16]

Based on the allocation concealment, Study conducted by Ahuja and colleagues had an unclear risk of bias because it stated that this trial does not mention the allocation method[17] Article from Goodacre et al had a low risk of bias because the allocation treatment pack was kept in the emergency department.[19] In Motamed et al, neither the patient nor personnel was granted access to data unless the patient discontinued the research. In Hossein et al, Emergency Physicians were blinded to protocol and allocation of treatment.[18] Article from Gallegos et al shows that allocation was prepared by the physician outside the study.[16]

In the aspect of blinding of participants and personnel, the study from Ahuja et al has a high risk of bias because it used a single-blinded method.[17] The rest of the articles used a double-blinded method in their research. In the blinding of outcome aspect, all of the articles have a low risk of bias. Ahuja et al used a prespecified protocol plan. Goodacre et al observed the outcome sequentially after intervention based on the time previously allocated.[19] The observer in Hossein et al is a blinded emergency physician.[18] Motamed et al used blinded nurses and physicians to become observers. The research was also executed in a prespecified protocol plan.[20]

From the detection of attrition bias, almost all of the studies have a low risk of bias. There is no missing data in the research from Ahuja et al.[17] Missing data in Goodacre et al is below 10%.[19] In Motamed et al, three of 148 subjects discontinued the study.[20] Hossein et al reported all data.[18] However, Gallegos et al have a high risk of bias because almost half of the data was excluded.[16] In the selective reporting parameter, all the article has a low risk of bias. However, an article from Motamed et al did not report complete data such as standard deviation. [20]

Goodacre et al and Gallegos et al show the effectiveness of inhaled magnesium in reducing readmission rates.[16,19] Three RCTs from Ahuja et al, Gallegos et al, and Hossein et al evaluate the effect of inhaled magnesium on patients'

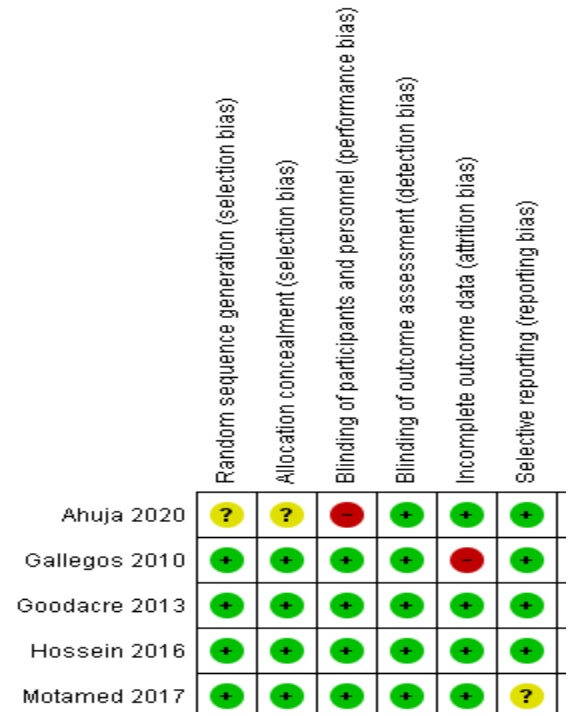

Figure 2. Risk of bias.

vital signs.[16,17,19] Two RCTs from Ahuja et al, and Hossein et al study the effect of inhaled magnesium on the severity of the disease.[17,18]

Studies from Ahuja et al, Gallegos et al, and Hossein et al evaluated the effect of inhaled magnesium on oxygen saturation with total subjects of 225 people. The dose of magnesium varies between 200-333 milligrams. This study showed no significant difference with the addition of inhaled magnesium compared to standard therapy in terms of oxygen saturation level (SMD 1,82; 95% CI -0.89 to 4.53; p =0.19 with random effect model). There was substantial heterogeneity of data in this study I^2=82% (**Figure 3**).[16,17]

Two studies were included in the meta-analysis about the effect of inhaled magnesium on respiratory rate (Ahuja et al and Hossein et al) with total subjects of 165 people.[17,18] Respiratory rates in both studies were measured after 60 minutes of administration of inhaled magnesium. The administration of inhaled magnesium compared to standard treatment improves the respiratory rate of an asthmatic patient (SMD -1,72; IK 95%: -3,1 to -0.35; p= 0.01) with a fixed effect model. Both studies did not have substantial heterogeneity with p=0,37 and I^2=0%. (**Figure 4**)

In the aspect of lung function, there are five studies included. Four of them show that patients' lung function improves after administration of inhaled magnesium. Two of them (Ahuja et al and Hossein et al) were statistically significant.

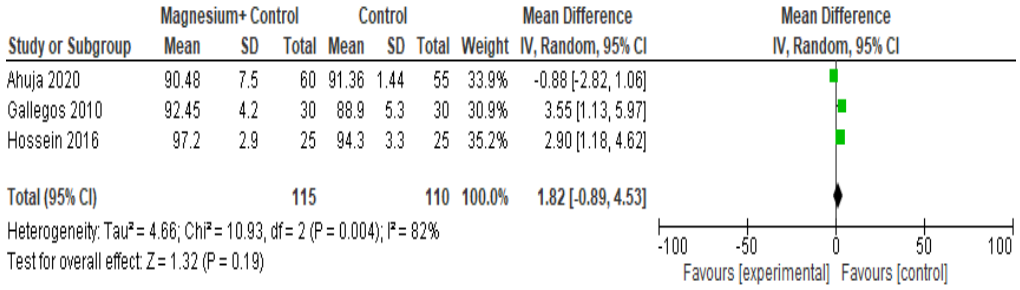

Figure 3. Meta-Analysis on oxygen saturation.

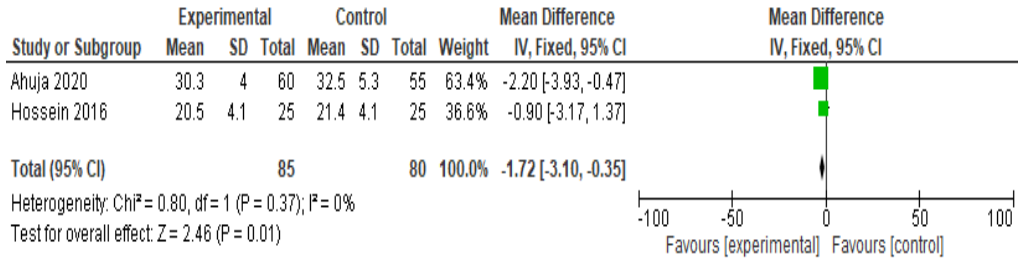

Figure 4. Meta-analysis on respiratory rate.

Table 1. Effect of Magnesium in Lung Function.

	Magnesium Group	Control Group	OR (95% CI)	P	N
Goodacre et al [30] 2013					
ΔPEFR (120 minute)	13.4% (18.0)	14.4% (17.4)	-0.6% (-3.4%-2.1%)	0.652	690
Abuja et al 2020[16]					115
PEFR (60 minute)	108±32	74.5± 19.3		<0.001	
PEFR (120 minutes)	189.3±47.0	103.3± 42.3		<0.001	
Motamed et.al, 2017[31]					148
PEFR 60 minute	333 l/min	280 l/min		NA	
FEV (60 minutes)	2.8 l /min	2.24 l/min		NA	
Gallegos et.al, 2010[10]					60
FEV (60 minutest)	2.16 ± 0.66 l/min	2.01± 0.51 l/min)		NS	
FEV *predicted*	69.7± 13.3 %	61.1 ± 12.7%		<0.01	
Hossein et.al, 2016[33]					55
PEFR *predicted* (60 min)	48.7±23.4 %	36± 28%		0.002	

However, the author only narratively presented because the parameters among the studies were different (**Table 1**).[17,18]

In the aspect of clinical severity, a study from Goodacre et al used dyspnea Visual Analog Scale (VAS) as the parameter. This study shows that magnesium therapy decreased dyspnea VAS in asthmatic patients, however, the difference was not statistically significant (VAS -2.6; -7 to 1.8 mm; p = 0.253).[19] Motamed et al used the Borg Dyspnea Scale as the parameter and it shows statistical improvement in clinical severity in the inhaled magnesium group (p=0.001).[20] However, Motamed et al did not report the exact number of Borg Dyspnea Scale. Ahuja et al and Hossein et al used subjective preferences of patients (yes or no) as parameters to measure the improvement of dyspnea.[17,18] Both studies show that people in the magnesium group have an improvement in clinical severity (RR 0.29; 95% CI 0.17 to 0.69; p = 0.001). Heterogeneity from both studies was statistically non-significant (p=0.87 with I^2=0%.) (**Figure 5)**

In the aspect of readmission rate, two studies were included in this review. Both of them are Goodacre et al and Gallegos et al. The total sample is 750 people.[16,19] There is no significant difference in readmission rate in the magnesium group compared to the control (RR 1; 95% CI 0.92 to 1,08; p= 0,96 and MD 1,82) (**Figure 6)**

The side effect of magnesium is analyzed by two studies from Ahuja et al and Goodacre et al with a total subjects of 805. A study from Goodacre et al shows that 52 out of 332 people in the magnesium group feel the side effects.[19] The example of side effects such as flushing 1%, hypotension 9%, nausea 2% and vomiting 2%. On the other hand, the side effects in the control group are flushing 1%, hypotension 6%, nausea 2%, and vomiting 1%. A trial from Ahuja et al shows no side effects in either group.[17] (Hazard Ratio 1.56; 95% CI 1.05 to 2.32; p= 0.03) using a *fixed effect model.* Heterogeneity from both studies cannot be analyzed.

DISCUSSION

To our knowledge, this is the first systematic review in the adult population to evaluate the effectiveness of inhaled magnesium for asthma in terms of readmission, clinical severity, lung function, and vital signs. In terms of readmission rate, there was no significant difference between the magnesium group and the control group (SMD 1,82; 95%CI to 0.89 - 4.53; p =0.19) with the random effect model. The reason for this phenomenon is magnesium only works within hours (half of life 8.3 hours).[21] The effect of inhaled magnesium on controlling asthma is still questionable. Meral et al show that the effect of inhaled magnesium as a bronchodilator starts one hour after inhalation, and its effect lasts for six hours.[22]

Vital signs of asthmatic patients that were observed in this review are respiratory rate

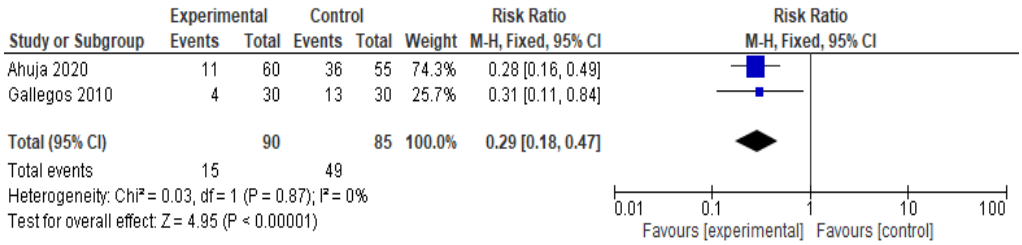

Figure 5. Meta-analysis on clinical severity.

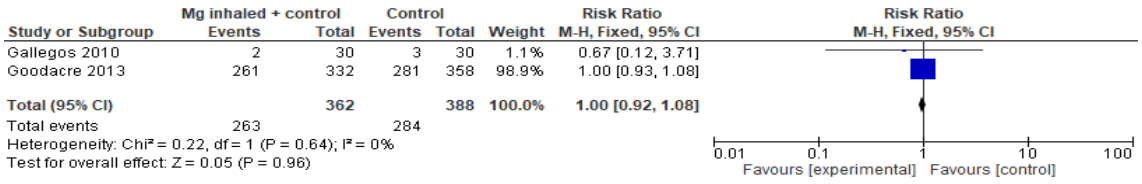

Figure 6. Meta-analysis on readmission.

oxygen saturation and blood pressure just reported in one trial. The trial showed that the administration of magnesium inhalation compared to standard treatment does not affect the oxygen saturation of asthmatic patients. The reason is the administration of oxygen influences the oxygen saturation. All the oxygen treatment was given to achieve oxygen saturation level in the patient. Schuh et al also showed that inhaled magnesium did not affect oxygen saturation.[23]

The administration of inhaled magnesium compared to standard treatment improves the respiratory rate of asthmatic patients. According to Busuttil, nebulized magnesium was beneficial for the stabilization of airway hyperresponsiveness. Inhaled magnesium might decrease bronchoconstriction in stable asthmatic patients. [24]

In the aspect of clinical severity, there are several parameters used by the clinical trials. Goodacre et al show that dyspnea VAS in asthmatic patients was decreased although it is statistically non-significant. Motamed et al showed that improvement in clinical severity in the inhaled magnesium group, although this clinical trial did not report the exact number. Ahuja et al and Hossein et al showed that the magnesium group has an improvement in clinical severity using the random effect model. On the whole, inhaled magnesium improves the clinical outcome of asthmatic patients. According to Knightly et al, the addition of inhaled magnesium in children and adults improves the clinical severity of asthmatic patients.[25]

Nearly all clinical trial results suggested an increasing number of lung functions. This result was supported by a systematic review from Knightly et al showing the promising result of inhaled magnesium.[25] Shan et al also showed that the addition of nebulized magnesium in salbutamol improved lung function.[26] According to Busuttil et al, the combination of inhaled magnesium and SABA has improved lung function in asthmatic patients. A small trial showed inhaled magnesium in combination with inhaled salbutamol and intravenous corticosteroid, to improve airway obstruction and reduce admissions relative to standard bronchodilator therapy.[23]

There is a slight increase in the rate of side effects in terms of hypotension and vomiting (9% vs 6%;2% vs 1% respectively). However, the percentage of side effects was relatively low (below 10%), inhaled magnesium was considered to be safe for asthma. In this case, clinicians should be aware of the side effects and then they should inform the patients. According to Powell et al, there was no good evidence suggesting the use of inhaled magnesium sulfate as a substitute for inhaled short-acting beta agonist (SABA) in first-line therapy.[27] Magnesium appeared to have a positive effect if it is used for last-line treatment due to its synergistic effect with SABA.[28]

CONCLUSION

Inhaled magnesium improves the outcome of asthmatic patients, especially in lung function, clinical severity, and respiratory rate. Moreover, inhaled magnesium is safe to be given.

CONFLICT OF INTEREST

The author declares no conflict of interest

FUNDING

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Supplementary Table. Study characteristics.

Author, Year of Publication Design Study	**Sample Number. Place of Study**	Outcome Measurement	Intervention	**Control**	Sex	Age	**Outcome of Study**	Additional Outcome
Goodacre et.al[30], 2013, *Randomized Controlled Trial*	N:690, Part of 3 Mg Trial in 34 Emergency Department, England	120 minutes after initial therapy For readmission 7 days after admission	MgSO4 500 mg + Salbutamol 5 mg + Ipratropium bromide 500µg + Oral Prednisolone	Salbutamol 5mg + Ipratropium bromide 500µg + Oral Prednisolone	Magnesium Female: 232 Male: 100 Control Female: 252 Male: 106	Magnesium: Median 35(23-47) Control: Median 34.5 (24-47)	There is no association between magnesium and readmission OR 0.96 (0.65-1.4). There is no association between dyspnoea VAS and magnesium -2.6 (-7 to 1.8) There is no statistical difference between inhaled magnesium and ΔPEF -0.6% (-3.4 to 2.1%). There is a higher risk of side effects in the magnesium group. OR 1.67 (1.05-2.66) p=0-0.31)	The side effect of inhaled magnesium is 12% compared to control (10%) In both groups, 1% of patients required ventilation respectively.
Ahuja et, al, [32] 2020, *Single-Blind Randomized Control Study*	N: 115, ED Patient in Karachi	Respiration rate, FEV, and oxygen saturation measured 30,60, 90 dan 120 minutes after the administration of magnesium	MgSO4 333 mg + Salbutamol 2.5 ml + Ipratropium bromide 250 mg + Hydrocortisone 100 mg	Salbutamol 2.5ml + Ipratropium bromide 250 mg + Hydrocortisone100 mg	115 patients Female: 64 Male: 51	N/A	In the 60th minute, the mean respiratory rates in the magnesium and control group are 30.3 and 32.4 times per minute, respectively. In the 120th minute, the mean respiratory rates in the magnesium and control group are 27.4 and 32.16 times per minute respectively (P = 0.003). The mean heart rate in the magnesium and control group are 109.87 and 122.11 times per minute respectively. There is an increasing FEV inpatient in patients with magnesium compared to control (189 and 103, respectively) (P<0.001) The mean of oxygen saturation in the magnesium and control group (90.62 and 91% respectively) Approximately, 72% of patients in the magnesium group feel better after administering drugs. 28% of patients in the control group feel better after administration.	

Motamed et al (2017)[31] *Randomized Controlled Clinical Trial*	N=148, Age 18-65 years old Emergency Department in Iran	PEFR dan FEV1 of patients. It is observed 20,40, and 60 minutes after admission	MgSO4 300 mg + Albuterol 2,5 mg + Ipratropium bromide 0,5 mg + Prednisolone 0.5 mg	Albuterol 2,5 mg + Ipratropium bromide 0,5 mg + Prednisolone 0.5 mg	N/A	Control Median 34.97 (19-60) Magnesium Median 36(21-63)	The mean PEFR of the Magnesium group is 333 L /minute and the Control Group is 280 l/minute (P<0.001). The mean FEV of the magnesium group is 2.8 L per minute and the control group is 2.24 L/min The Borg Dyspnoea scale in the magnesium group is better than the control group (P<0.001). The trial shows no exact number of Borg Dyspnoea scale	
Gallegos et al (2010)[10] *Placebo-controlled, double-blinded clincal trial*	N= 60 Patient above 18 years old. Tertiary Hospital in Meksiko	FEV, readmission rate, Severity of Symptoms	MgSO4 333 mg (3x) + Methylprednisolone 125 mg + Albuterol 7.5 mg + Ipratropium Bromide 1.5 mg	Methylprednisolone 125 mg + Albuterol 7.5 mg + Ipratropium Bromide 1.5 mg	Control Male: 9 Female: 21 Magnesium Male: 9 Female: 21	Control Mean:34.3+/-12.4, Magnesium: Mean 40.2+/ 11	The readmission rate of the control group is 10%, and magnesium group is 7% FEV in the magnesium group is 2.16+/- 0.66L per minute compared to control 2.01+/- 0.51. The relieving of symptoms in the magnesium group occurred in 26 of 30 participants. The relieving of symptoms in the control group occurred in 17 of 30 participants. Oxygen Saturation in the magnesium group is higher than control (92+/- 4.2 and 88.9+/-5.3, respectively)	Side effects that people feel like bitter taste in their mouth and nausea (Not mentioned in the study)
Hossein et al, 2016[33] Randomized Controlled Trial	N=50, Two Emergency Centres in Iran Patient above 16 years old.	Dyspnoea Severity Score, PEFR, Respiration rate, Oxygen Saturation	MgSO4 200 mg (3x) + Salbutamol 2.5 mg + Atrovent 0.5 mg + Oral Prednisolone 50 mg	Salbutamol 2.5 mg + Atrovent 0.5 mg + Oral Prednisolone 50 mg	Magnesium: Male: 14 Female 11 Control Female: 11 Male: 14	Magnesium Mean: 52.4+/16.9 Control Mean: 53+ /- 16.2	The mean respiratory rate in the magnesium group is 20.5±4.8 and the mean of oxygen saturation of the control group is 21.4±4.1 (P =0.229) The mean of oxygen saturation in the magnesium group is 97.2±2.9 and the mean of the oxygen saturation control group is 94.3±3.3 (P <0.001) The mean of PEFR in the magnesium group is 48.7±23.4 and the mean of a control group is 36±28.7 (P <0.002)	

Proportion of Hypogonadism in Transfusion-Dependent Thalassemia Patients and Its Contributing Factors

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ABSTRACT

Background*: Beta thalassemia is a lifelong disease involving malformed red blood cells (RBC). One of the disease's complications is hypogonadism, in which adults tend to exhibit regression in sexual characteristics, experience sexual dysfunction, and therefore have a lower quality of life. Around 3-10% of the Indonesian population carries the beta-thalassemia gene. This study aimed to see the proportions of hypogonadism in transfusion-dependent thalassemia patients and its contributing factors.* ***Methods****: This is a cross-sectional study involving 60 male patients admitted to three Indonesian general hospitals from July 2022 to July 2023. All patients were diagnosed with beta-thalassemia via chromatography hemoglobin analysis. We performed a single-time physical examination and laboratory examinations to determine FSH, LH, and free testosterone levels. The correlation between Hb and sexual hormone levels was analyzed using Spearman's rank correlation coefficient. ROC curve analysis was conducted afterward. All statistical analysis was done in SPSS version 29.* ***Results****: 31 out of 60 thalassemia patients had hypogonadism. Pre-transfusion Hb count was found to be linearly correlated with FSH (r = 0.388, p = 0.049), LH (r = 0.338, p = 0.008), and free testosterone (r = 0.255, p = 0.049). ROC analysis indicated that pre-transfusion Hb was viable as a predictor for hypogonadism (AUC = 0.655, 65.5% sensitivity, 67.7% specificity).* ***Conclusion****: We confirmed the role of pre-transfusion Hb count as a potential predictor for hypogonadism due to the tissue hypoxia mechanism and transfusion-related iron overload in TDT patients. Decreased Hb is linearly correlated with FSH, LH, and testosterone levels. Decreased Hb also downregulates these factors.*

Keywords**:** *Pre-transfusion hemoglobin, hypogonadism, transfusion-dependent thalassemia.*

INTRODUCTION

Beta thalassemia is a hematological disorder in which the body's erythrocytes become malformed. In Indonesia, approximately 27 million people are thalassemia gene carriers.[1] One of the common complications is hypogonadism, where the body's sex glands produce little to no hormones. Hypogonadism detection is important due to thalassemia often being diagnosed during adolescence.[2]

Based on demographic, community, or screening investigations, the incidence of hypogonadism ranges greatly, from 2.1 to 12.8%.[3] Nonetheless, the transfusion-dependent thalassemia (TDT) population has an incidence rate of hypogonadism that approaches 70%.[4,5] This is thought to be due to the accumulation of iron in endocrine organs such as the pituitary and testes which can lead to organ toxicity, and cause impaired hormone secretion in these organs.[6,7]

Several mechanisms are thought to play a role in the incidence of hypogonadism in thalassemia patients, not only due to reproductive hormones but also other mechanisms such as adipose tissue, leptin, body mass index (BMI), and pre-transfusion hemoglobin (Hb). TDT patients often require routine transfusion, and it is recommended that TDT maintain a hemoglobin range of 9–10.5 g/dL.[3] In addition, failure to maintain hemoglobin count is known to cause complications due to tissue hypoxia.[4]

However, there is little information available on the pathomechanism of hypogonadism in TDT patients. Serum ferritin is not necessarily linked to TDT, despite being considered to be the cause of hypogonadism. GnRH examination that cannot be examined at the periphery causes an unclear understanding of the pathway of hypogonadism. Our study aims to describe the proportions and risk factors of hypogonadism among TDT patients in Indonesia.

METHODS

We performed a cross-sectional study among thalassemia patients aged 18 years and older who were admitted to the Thalassemia Clinic in either Cipto Mangunkusumo General Hospital in Jakarta, Fatmawati General Hospital in Jakarta, or Hasan Sadikin General Hospital in Bandung, Indonesia, between July 2022 and July 2023. All patients were reviewed by a hematologist to confirm their beta-thalassemia diagnosis via hemoglobin analysis and high-performance liquid column chromatography.

This study uses a cross-sectional design. Patients with transfusion-dependent thalassemia who are male, older than eighteen, diagnosed by pediatricians or internists, and who are willing to take part in the study are enrolled. Individuals with mental disorders, those using drugs that cause hyperprolactinemia, those who have had hypophyseal surgery in the past, those who have a hypophysis tumor, those who have had diabetes mellitus, testicular trauma, radiation, or enlargement, and those who have received testosterone therapy within the last two weeks were not included. Subjects included during July-August 2023 in Thalassemia Polyclinic in Cipto Mangunkusumo Hospital Jakarta, Thalassemia Polyclinic in Fatmawati Hospital Jakarta, and Hematology-Oncology Polyclinic in Hasan Sadikin Hospital Bandung.

Demographic parameters included patients' age, thalassemia type, history of splenectomy, and history of iron chelator consumption. Laboratory examinations for hypogonadism include FSH, LH, and free testosterone levels. Patients were considered hypogonadal if the free testosterone level was < 5pg/mL. We exclusively selected male participants to eliminate any hormone fluctuations caused by the menstrual cycles of female patients. Hemoglobin data were assessed as the patient visited the hospital and before they underwent transfusion.

The association between Hb count and FSH, LH, and free testosterone levels was analyzed with Spearman's correlation analysis. Additionally, the ROC curve was used to identify the diagnostic efficacy of pre-transfusion Hb count for hypogonadism and its cutoff value. A p-value of less than 0.05 was considered statistically significant. All data processing was performed using SPSS 29.0.

This study does not include interventions for the patient that would otherwise be regulated by the Declaration of Helsinki. The study's aim

and goals were explained clearly to the patients and their families; afterward, the patient or their families signed a consent form. This study was approved by the Faculty of Medicine Universitas Indonesia's ethical board on May 9, 2022, with registration number KET-435/UN2.F1/ETIK/PPM.00.02/2022.

RESULTS

Our study involved 65 patients in total, of whom 5 were excluded for various reasons (Fig 1), resulting in 291 subjects being included in the final analysis. All participants had given their consent to be part of this study and were confirmed to have thalassemia. The characteristics of these subjects are presented in **Table 1**. Subjects had a median age of 22 (18 - 42) years old. The proportion of hypogonadism was 51.1%.

To determine hypogonadism, which has various signs and symptoms, we assessed both clinical manifestation and laboratory examination to accurately represent the hypogonadism found in our patients.

Overall, we have established that among this study's participants, signs of hypogonadism were prominent in at least half of the patients based on their clinical features alone. In addition, Tanner staging to objectively determine sexual growth delays.

To confirm the presence of hypogonadism in patients, our study also conducted laboratory examinations on the participants to determine their hormone levels. Our results are described in **Table 2**.

Subsequently, we performed ROC curve analysis and found that pre-transfusion hemoglobin count could be used to verify clinical diagnosis of hypogonadism with a cutoff value < 8.75 g/dL (AUC = 0.655, 65.5% sensitivity, 67.7% specificity).

DISCUSSION

We found that 51.1% of the subjects experienced hypogonadism compared to similar studies in other countries.[5] Moreover, low pre-transfusion Hb, high FSH, and high leptin were associated with an increased risk of hypogonadism.

The distribution of pubic hair in this study appeared to be sufficient at the tanner stage IV-V level, with a distribution as high as 53.4%. Meanwhile, the other 46.6% of subjects had less or no pubic hair growth. A popular physical test for determining puberty is the Tanner stage. This examination assesses a person's secondary sex characteristics. Tanner stage and testosterone levels have a significant positive association, according to research by Balzer et al. Several factors, including pubic hair, testicular length, and testicular volume, are evaluated during the Tanner stage itself. At least at stages IV and V, the Tanner stage is believed to have grown

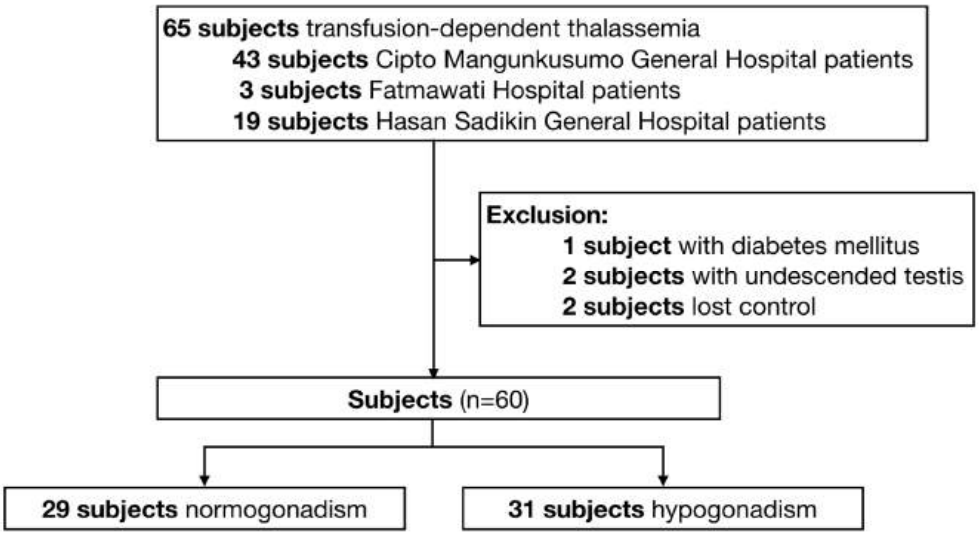

Figure 1. Flow diagram summarizing the subject recruitment process.

Table 1. Clinical characteristics.

Characteristics	Total (n = 60)
Age (year), median (min-max)	22 (18-42)
Clinical manifestation, n (%)	
Family history of delayed sexual development	
Yes	0 (0)
No	60 (100)
Erectile dysfunction	
Yes	51 (85)
No	9 (15)
Decreased libido	
Yes	3 (5)
No	57 (95)
Physical examination, n (%)	
Body Mass Index (kg/m^2), mean (SD)	18,63 + 2,45
Underweight (BMI < 18.5 kg/m^2)	32 (53)
Normoweight (BMI 18.5 – 22.9 kg/m^2)	24 (40)
Overweight (BMI 23 – 24.9 kg/m^2)	3 (5)
Obese (BMI >25 kg/m^2)	0 (0)
Abnormally high-pitched sound	
Yes	24 (40)
No	36 (60)
Presence of pimples	
Extensive	30 (50)
Minimal	30 (50)
Presence of facial hair (mustache and beard)	
Extensive	35 (59)
Minimal	25 (41)
Presence of armpit hair	
Extensive	37 (61)
Minimal	23 (38)
Spleen size	
Not palpable	3 (5)
Schuffner 1 – 4	43 (71)
Schuffner 5 – 8	8 (13)
Post-splenectomy	6 (10)
Flaccid penile length (cm), median (min-max)	7 (4 – 8)
Orchidometer testicle size (ml), mean (SD)	11 ± 6
Tanner stage, n (%)	
I	13 (21.7)
II	6 (10)
III	9 (15)
IV	25 (41.7)
V	7 (11.7)

SD: standard deviation, BMI: body mass index.

Table 2. Laboratory examination.

Parameters	Median (min-max) Total (n = 60)
Pre-transfusion Hb (g/dL)	8.7 (5.1 - 14.2)
Leptin (pg/mL)	1,942 (242-22,270)
FSH (mIU/mL)	8.3 (0.1 - 46.1)
LH (mIU/mL)	18.1 (0.5 – 80.8)
Free testosterone (pg/mL)	4.7 (0.1 - 35.78)
Hypogonadism	31 (51.6%)

Hb: hemoglobin, FSH: follicle stimulating hormone, LH: luteinizing hormone.

Table 3. Bivariate analysis of association between independent variables and hypogonadism.

Variables	Normogonadism (n=19)	Hypogonadism (n=31)	p
BMI (kg/m$^{2)}$	17.7 ± 1.9	19.3 ± 2.6	0.122
Pre-transfusion Hb (g/dL)	8.9 (6-12.6)	7.2 (5.1-14.2)	0.569
FSH (mIU/mL)	8.09 (3.65-24.3)	12.4 (0.1-46.1)	0.040
LH (mIU/mL)	18.1 (6.95)	27.8 (0.5-90.8)	0.005
Leptin (pg/mL)	1,405 (411-5,089)	3,616 (242-22,270)	0.053

BMI: body mass index, Hb: hemoglobin, FSH: follicle stimulating hormone, LH: luteinizing hormone.

Table 4. Multivariate analysis of association between independent variables and hypogonadism.

Variables	OR	p-value
Model 1		
BMI	1.112	0.606
Pre-transfusion Hb	0.571	0.033*
FSH	1.086	0.146
LH	1.017	0.568
Leptin	1.001	0.013*
Model 2		
Hb	0.575	0.035*
FSH	1.084	0.154
LH	1.018	0.540
Leptin	1.001	0.003*
Model 3		
Hb	0.573	0.033*
FSH	1.110	0.019*
Leptin	1.001	0.003*

BMI: body mass index, Hb: hemoglobin, FSH: follicle stimulating hormone, LH: luteinizing hormone. *Statistically significant.

to adult size. This study found a significant correlation between pre-transfusion Hb count and its downregulating effect on sexual hormones associated with hypogonadism.[6]

Among our participants, FSH levels tended to be within the normal range of 1.5–12.4 mIU/mL. Conversely, LH levels were usually elevated, with the highest value being recorded at 80.8 mIU/mL. Furthermore, free testosterone levels tended to be very low across all ages. The elevated LH and decreased testosterone levels suggested that most of the participants had primary hypogonadism. In a similar study regarding the sexual characteristics of female beta thalassemia major patients, fully developed adults tended to exhibit sexual dysfunction and a regression,[7] a finding that supports our physical examination results.

Our study shows that pre-transfusion Hb count is directly correlated to FSH, LH, and free testosterone levels, suggesting that lower Hb counts impair sex hormone levels. Similar studies have associated endocrinopathies with post-transfusion iron overload and its subsequent deposition in visceral organs.[8,9] Several studies were in agreement with our study and proposed that the occurrence of hypogonadism is likelier in TDT patients with lower pre-transfusion Hb counts (OR 0.38, 95% CI [0.145 – 0.994]).[10,11] One study supported this by elaborating that thalassemia complications could also be caused by chronic tissue hypoxia due to low baseline Hb count. Low testosterone impairs erythropoiesis via inadequate stimulation to erythropoietin (EPO) secretion and decreased erythroid progenitor cell formation.[12,13] Therefore, EPO also exacerbates thalassemia in a positive feedback loop manner, which is consistent with our findings that the patients had low testosterone levels and low Hb counts.

We also establish the potential of pre-transfusion Hb count as a reliable predictor for hypogonadism clinical diagnosis with a resulting AUC of 0.655. The cutoff of 8.75 g/dL is also reasonably low without compromising tissue perfusion, which usually falls below 7-8 g/dL.[14,15] Another study found that a Hb countless to or equal to 6.81g/dL could predict hypogonadism in TDT patients (AUC = 0.708, 66.7% sensitivity, 63.4% specificity) with findings that are quite similar to our results.[10] Furthermore, since 8.75 g/dL is categorized as moderate anemia, it is possible that consistently impaired perfusion may slowly damage gonadal tissues over time. Furthermore, it is known that lower Hb counts in thalassemia patients indicate ineffective erythropoiesis and increased hemolysis.[10] Several studies provide support for these results; it has been found that thalassemia increases oxidative damage by inducing a hypercoagulable state, coupled with excessive tissue iron and chronic hypoxia,[2,16] which in turn causes impaired steroidogenesis in primary hypogonadism and gonadal insufficiency in secondary hypogonadism.[7]

Multivariate studies have agreed that pre-transfusion Hb count is an important parameter for determining quality of life for both TDT and NTDT due to its correlation with various complications, including hypogonadism.[10,11] However, to the best of our knowledge, this is one of the first studies to explore the potential of Hb count as a predictor for hypogonadism as a thalassemia complication. By knowing pretransfusion Hb as a predictor of hypogonadism in transfusion-dependent thalassemia patients, it is anticipated that patients can achieve the recommended Hb target, either with an adequate number of transfusion packs, or an adequate transfusion frequency.

Our investigation showed an association between leptin and an increased risk of hypogonadism (OR 1.001, p = 0.003). This finding was consistent with a study by Lima et al.[17] Leptin seems to control testicular cells, which in turn controls male reproduction, independent of the GnRH central regulatory route. Leptin can affect steroidogenic processes because it is known to be able to penetrate the blood testis barrier. Leydig cells appear to be the only place where leptin receptor (LPR) expression occurs in the gonads of males. The levels of LPR are negatively connected with testosterone levels as well as anomalies in sperm quality and production. Testicular tissue is primarily affected by leptin through the activation of the signal transducer and activator of the transcription 3 (STAT3)/Janus kinase 2 (JAK2) pathway.[18]

The main limitation of this study lies in its cross-sectional design, which does not represent a causal effect. This study design may have confounding variables that we did not analyze with a multivariate analysis. On the other hand, the study's main strength is that it is among the first to correlate and discover the potential of pre-transfusion Hb count potential as a predictor for hypogonadism using ROC curve analysis. Our results are in agreement with the previous study.

In conclusion, we identified the measurement of pre-transfusion Hb as a potential diagnostic approach that may be widely used to predict hypogonadism in thalassemia patients due to its cheap cost and high practicality. This is especially true in Indonesia, where primary health facilities can conduct peripheral blood counts.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest.

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Significant Inverse Correlation of Serum Levels of Osteoprotegerin (OPG) and Transferrin Saturation in Thalassemia Dependent Transfusion (TDT) Patients

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ABSTRACT

Background: *Osteoporosis is a major problem in transfusion-dependent thalassemia patients (TDT) patients. Osteoprotegerin (OPG) is one of several bone markers that are closely associated with osteoporosis in TDT patients. OPG is a glycoprotein that functions as a feedback receptor for the Receptor Activator of Nuclear Factor kappa B Ligand (RANKL), which is an alpha tumor necrosis factor receptor. One of the causes of decreased bone mass density is iron toxicity, which can be identified by showing elevated transferrin saturation. Bone mass dual X-ray absorptiometry (DEXA) is a gold standard for the diagnosis of osteoporosis, these procedures are not commonly available in Indonesia. This study was conducted to analyze the correlation between serum levels of OPG and transferrin saturation in TDT patients.* ***Methods:*** *A correlational study with a cross-sectional approach analyzed data from TDT patients at Hemato-Oncology Medic Outpatient Clinic, Hasan Sadikin General Hospital, Bandung, Indonesia. Primary data were obtained through blood sampling and anthropometry measurement while secondary data were obtained from the patient's medical records. OPG and transferrin saturation levels were assessed using the ELISA method. Research data were analyzed using the rank Spearman correlation test.* ***Results:*** *Data were collected from 51 research subjects (30 women dan 21 men). The median OPG level was 380 (170-1230) pg/mL and the median transferrin saturation level was 89.4 (66.7 – 96.2)%. Analysis of correlation showed a significant correlation between and transferrin saturation level with a coefficient value of r -0.539 and p-value <0.001.* ***Conclusion:*** *There was a significant inverse correlation between OPG with transferrin saturation in TDT patients.*

Keywords**:** *OPG, transferrin saturation, osteoporosis, transfusion-dependent thalassemia.*

INTRODUCTION

Osteoporosis is the most common complication associated with transfusion-dependent thalassemia (TDT) patients.[1] The pathogenesis is multifactorial and mainly includes bone marrow expansion, endocrine dysfunction, and iron overload.[2] The exact mechanisms by which these variables cause bone loss are still unclear.[3,4] A meta-analysis by Charoenngam et al. reported that the pooled prevalence of fracture among patients with thalassemia was 16%, with subgroup analysis describing prevalences of 18% and 7% in patients with TDT and NTDT, respectively.[5] Between 28% and 32% of people in Indonesia have osteoporosis or low bone density.[6] In the meantime, thalassemia's bone problem has a detrimental psychological effect, reduces the quality of life, and raises treatment costs.[7]

Thalassemia bone disease (TBD) is a unique bone disease that can impact all elements of bone structure and quality, as well as mineral density. Osteoporosis, fractures, spinal abnormalities, compression of the nerves, and pain are among the worst morbidities associated with TBD. It has become a major challenge to control the rising morbidity burden brought on by the severe thalassemia phenotype.[8] The hypothalamic-pituitary-gonadal axis malfunction, growth hormone effects on the parathyroid gland, diabetes, hypothyroidism, inefficient hemopoiesis, and direct iron toxicity to osteoblasts are a few of the aetiological causes for thalassemic osteoporosis. Because iron chelation treatments affect cartilage tissue, they may potentially contribute to osteopenia and osteoporosis.[8,9] Osteoprotegerin (OPG) and the receptor activator of nuclear factor-kappa β (RANK)/receptor activator of nuclear factor-kappa β ligand (RANKL) are the major cytokines related to the regulation of bone resorption.[10] The final major modulator of osteoclast activation and proliferation has been identified as the receptor activator of the nuclear factor-kappa β (RANK)/RANKL/OPG pathway.[10-12] Regular blood transfusions have been demonstrated to improve the survival of patients with thalassemia; at this point, they also raise the risk of iron excess and iron toxicity. One of the elements that lead to organ damage in thalassemia is non-transferrin-bound iron (NTBI), a free radical that mediates iron toxicity.[9,13] NTBI levels are only tested at a few research institutions abroad, therefore, surrogate markers such as serum ferritin and saturation transferrin have been used to measure iron toxicity.[7,9,14,15]

The measurement of bone mass dual X-ray absorptiometry (DEXA) in the lumbar area, femoral neck, and forearm is a non-invasive examination that accurately assesses bone density, however, these procedures are not widely available in Indonesia. Screening TDT patients with DEXA is necessary for detecting osteoporosis and improving bone health. Consequently, a need for bone markers exists.[7,10,16,17]

The biological effects of transferrin saturation and the OPG/RANKL system on a variety of metabolic bone diseases have been a focus of several developing investigations; nonetheless, the pathophysiology of bone disease in thalassemia remains entirely unclear.[9] These biomarkers are useful to provide the early assessment of osteoporosis when the BMD measurement of DEXA does not offer enough information to make the diagnosis.[7,16-17] Thus, the objective of the current study was to explore the serum levels of OPG and to detect their relations with transferrin saturation, as possible early predictors of the skeletal changes in TDT patients.

METHODS

This is a retrospective analysis. We collected the data from the medical records from TDT patients at the Hasan Sadikin Hospital Hematology-Medical Oncology Clinic Bandung, Indonesia from July to September 2023. This study was approved by the Health Research Ethics Committee, Faculty of Medicine Padjajaran University, and Dr. Hasan Sadikin Hospital Research Ethics Committee (No. DP.04.03/D. XIV.2.2.1/19547/2023).

The inclusion criteria were: (1) Age 18 years and over, (2) TDT patients who have medical record data. Patients with the following conditions were excluded from the study: (1) TDT patients including those who have never received iron chelation therapy, (2) TDT patients who had undergone a splenectomy procedure,

received steroid therapy with an equivalent dose of prednisolone 5mg during for more than 3 months. TDT patients with other comorbidities such as (1) infection disease, (2) liver disease, (3) hematological disorders, (4) diabetes mellitus, (5) chronic kidney disease, (6) bone disease, (7) hormonal disorders, (8) malnutrition, (9) vitamin D deficiency.

The blood samples were drawn from the vein by sterilized synergies with 5 milliliters. The sample was put in the labeled tube for blood to be used for preparing serum for the following biochemical and biomarkers. Blood was left at room temperature for 10 minutes for clotting, centrifuged at 6000 rpm for 10 minutes, and then serum was separated and frozen at -80 ºC until time for the laboratory analysis for the study.

The variables were BMI (Body Mass Index), the electronic balance and height device, were used for calculating the weight and height and applied the equation below: BMI = weight (kg)/height (m2). Biomarker measurement estimation human OPG the specific kit for measuring human OPG, and transferrin saturation levels in serum were supplied by (Elabscience-USA). The measurement of the human OPG ELISA (enzyme-linked immunosorbent assay-automated microtiter plate) kit was performed by (Elabscience-USA) sandwich immunoassay technique with a normal range between 160 -10.000 pg/ml.[18]

The characteristics of patients, for categorical data presented in frequency and proportion, and for numerical data, a normality test will be carried out using the Kolmogorov Smirnov test. Comparisons of categorical variables, expressed as proportions, correlations were evaluated using Rank Spearman's correlation coefficient. All statistical analyses were conducted using SPSS version 23.0 (SPSS, Chicago, IL).

RESULTS

There were 147 TDT patients at the Hemato-Oncology Medic Clinic Hasan Sadikin General Hospital from June 2021 to June 2022. A total of 51 patients were enrolled in this study (Figure 1), which consisted of 21 males (41,2%) and 30 females (58,8%) their median age was 22 which ranged from 19 to 44 years. The characteristics of the patients are presented in **Table 1**.

Based on **Table 1**, the median transferrin saturation was 89,4% with the lowest value of 66,7% and the highest value of 96,2%. These results showed that the serum OPG level with TDT was 380 pg/ml with the lowest value of 170 pg/ml and the highest of 1230 pg/ml (**Table 1**).

Table 2 shows a significantly negative correlation ($p<0.001$) between OPG and transferrin saturation ($r = -0.539$). The lower the OPG the higher the transferrin saturation measurement.

DISCUSSION

The result of this study indicated a significant negative correlation ($r = -0.539$) and ($p < 0.001$) between osteoprotegrin concentration with transferrin saturation in TDT patients which are shown in **Table 2**. Several author's studies indicated a significant decrease in the OPG concentration in a group of thalassemia major patients in comparison with the healthy group.[19-21] A Study by Alfaqih et al. showed

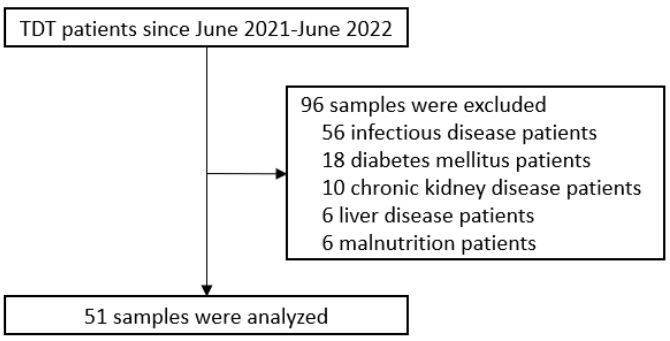

Figure 1. Flow diagram for transfusion-dependent thalassemia patients recruitment

Table 1. Characteristics of transfusion-dependent thalassemia patients.

Characteristics	N=51
Age, years (median)	22 (19 – 44)
Female, n (%)	30 (58.8)
Duration of thalassemia, years (median)	18 (10 – 35)
Frequency of blood transfusion median (min-max)	17 (6 – 38)
Blood transfusion volume (mL/kg/years) median (min-max)	168 (68 - 574)
BMI (kg/m^2)[a]	19.2 ± 2.6
Laboratory values	
Pre-transfusion hemoglobin (mg/dl)[a]	7,2 ± 0,8
Random blood sugar level (mg/dl), median (min-max)	114 (69-190)
Iron Status	
Fe serum (µg/dL), median (min-max)	216 (93 – 631)
TIBC (µg/dL), median (min-max)	247 (122 – 656)
Transferrin saturation (%), median (min-max)	89.4 (66.7 – 96.2)
Biochemical of bone marker	
OPG (pg/mL), median (min-max)	380 (170 – 1230)

Abbreviations: BMI, Body Mass Index; TIBC, total iron binding capacity; OPG, Osteoprotegerin
[a] Data are presented as the mean ± standard deviation

Table 2. Correlation of serum levels OPG and transferrin saturation in transfusion-dependent thalassemia.

Variables	Transferrin Saturation (%)		
	Coefficient r	Coefficient determinant r^2	P Value
OPG (pg/mL)	-0.539	0,29	<0.001*

Abbreviations: OPG, Osteoprotegerin.

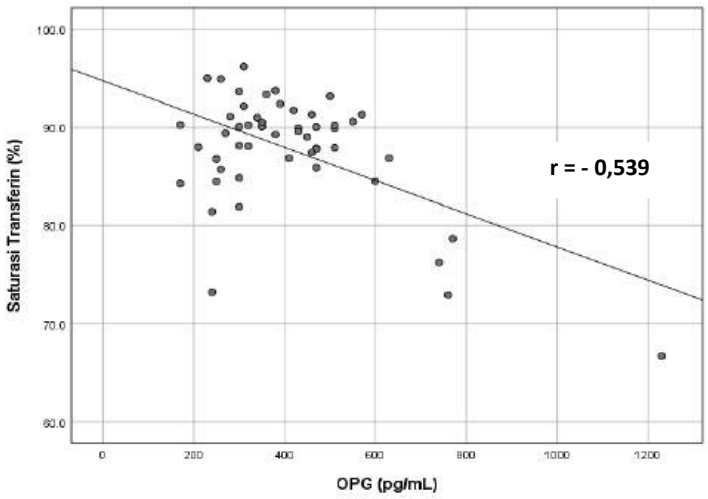

Figure 2. Scatterplot of serum levels OPG and transferrin saturation in TDT patients.

that RANKL concentrations were significantly higher in patients with thalassemia compared to the controls, but OPG concentrations were significantly lower in thalassemia patients. These results demonstrate that a dysregulated balance between the rate of bone resorption and bone production may be the cause of the dysregulated bone remodeling that occurs in thalassemia patients. It suggests that thalassemia patients have a net loss of bone due to a decrease in the rate of bone development correlated with an increase in the rate of bone resorption.[22] Several

studies have reported that in patients with thalassemia, endocrine effects, iron deposition, iron chelation therapy, or vitamin D therapy down-regulate osteoblasts, which are the primary generators of OPG. This results in an increase in RANKL and a decrease in OPG, which increases the risk of osteoporosis.[1-4] In contrast, another study indicated a significant increase in the OPG concentration in a group of TDT patients in comparison with a healthy group.[23] A Study by Hashemieh et al suggested that two cytokines, OPG and RANKL, have recently been recognized as important pacemakers in the pathogenesis of osteoporosis in TDT patients.[24] Many studies have demonstrated that NTDT patients have a significantly higher incidence of osteoporosis (81.6%) compared to TDT patients. This is related to a reduction or disruption of the bone architecture, which increases the risk of fractures, bone resorptions, decreased bone formation, and decreased bone mineral density (BMD).[25] Osteoporosis is an important problem for TDT patients. OPG was a bone marker that played a crucial role in the development of osteoporosis in TDT patients.[19-21]

TDT patients need frequent blood transfusions to control their chronic anemia. Iron overload is caused by repeated blood transfusions, increased hemolysis of red blood cells, and increased iron absorption in the gastrointestinal tract.[9] All body cells are very toxic to excess iron, which may result in major and permanent organic damage such as cirrhosis, diabetes, heart disease, hypogonadism, and osteoporosis. If untreated, these conditions can cause severe morbidity and death in TDT patients.[9] Sagare et al's study showed that transferrin saturation increased in both homozygous & heterozygous forms of thalassemia significantly as compared to control. This study showed that transferrin saturation may be the best way to utilize the information about iron overload & development of complications like oxidative stress due to non-bound iron form.[15] This study analyzed the correlation between OPG and transferrin saturation, the result showed that there was a negative and significant correlation between OPG with transferrin saturation in TDT patients. This is the first study to obtain a significant correlation between OPG and transferrin saturation in adult TDT patients. Atmakusuma et al's study showed that there was a significant correlation between bone mass density and transferrin saturation in adult patients with thalassemia. Although the correlation was weak, it was statistically significant.[7]

The pathogenesis of TBD is multifactorial, including age, gender, childhood growth retardation, bone marrow expansion, iron and chelator toxicity, physical inactivity, low body weight, nutritional deficiencies, and hormonal deficiencies, which are still not fully understood.[4] This study included 58.8% female TDT patients as participants. This was consistent with studies by Thavonlun et al and Koohmanaee et al who found that the incidence of thalassemia bone disease is more common in females.[3,4,19] Thavonlun et al's study showed that women tended to have fractures more than men. Thalassemia patients exhibit varying degrees of inefficient erythropoiesis, which are strongly correlated with the severity of genotype and clinical phenotype. Female sex was associated with an increased risk of osteoporosis.[3,4,19] The ages of the subjects in this study ranged from 19 years to 44 years with a median of 22 years. Wong et al study showed that the patient's comparatively young ages (mostly in their 20s and 30s), the variety of risk factors for bone loss (many specific to thalassemia patients), the frequency of fractures, and the reaction to therapy with bone-preserving medications are the aspects that differentiate this case. Adolescence is a crucial time for bone accretion, during which endocrinopathies (such as GH and sex hormones) and lifestyle factors—such as diet and exercise—play a crucial role in maximizing bone development and maintaining optimal bone health. The peak bone mass attained and the rate of bone loss thereafter are the primary determinants of BMD in young adults and beyond. TDT patients have a reduced ability to reach maximal bone mass.[26]

This study had limitations that could have an impact on the findings. Firstly, there was no hormonal assessment and its relation to bone mass density. Secondly, this study did not perform a BMD DEXA examination as a gold

standard examination. Lastly, this study was limited to a single center.

CONCLUSION

Based on the results, there was a significant inverse correlation between OPG with transferrin saturation in TDT patients.

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Health Literacy Among University Students in the COVID-19 Pandemic: A Systematic Review

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ABSTRACT

Background: *The purpose of this systematic review was to assess different studies that worked on university students' health literacy during covid19 pandemic and to make an overview of this issue to recognize possible determinants associated with health literacy.* ***Methods:*** *This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Four databases (Google Scholar, Web of Science, Pubmed, and Scopus) were used for searching cross-sectional works that assessed the health literacy of university students. We searched papers from December 1st, 2019 up to June 10th, 2022. English language articles were used. Studies were done in countries including; Iran, Pakistan, the USA, Vietnam, China, Colombia, Germany, and Indonesia.* ***Results:*** *The systematic review contains 12 research studies involving 17773 students. There was a relationship between health literacy and some determinants. Positive determinants included age, female gender, Urban background, cognitive maturity, Higher educational qualification, information source (Health workers), number of semesters, and parental education. Some negative determinants were male gender,*

Rural background, smoking, drinking, being able to pay for medication, lower conspiracy beliefs, and higher fear of COVID-19. ***Conclusion:*** *University students around the world should have courses about health literacy according to university disciplines. These courses should be available for students of different fields to enhance their effectiveness, and training should be associated with students' needs and their subgroup traits.*

Keywords**:** *COVID-19, Pandemics, Health Literacy, SARS-CoV-2.*

INTRODUCTION

Coronaviruses are important pathogens in both humans and animals. A novel coronavirus was reported as the source of a cluster of pneumonia cases in Wuhan, China's Hubei Province, at the end of 2019. It quickly spread throughout China, resulting in an epidemic and a global pandemic.[1] Cases have been reported on all continents since the cases were first reported in Wuhan. Over 500 million confirmed cases of COVID-19 have been reported worldwide.[2] The reported number of cases underestimates the overall burden of COVID-19, as only a small proportion of acute infections have been diagnosed and reported. Seroprevalence studies in the United States and Europe have reported the incidence of cases where previous exposure to SARS-CoV-2, which is reflected in seropositive, was reported after considering the possibility of false positives or negatives. It turned out that it exceeds about 10 times.[3-6]

To get the pandemic under control, people must follow public health measures like social isolation, vaccination, and hygiene. Such adherence necessitates health literacy, which is defined as the knowledge, motivation, and skills needed to understand, access, evaluate, and utilize health information in daily life to make decisions and judgments about healthcare, health promotion, and disease prevention to improve or maintain quality of life over time.[7]

Health literacy is and has been crucial not only in controlling infectious diseases but also in avoiding the devastation that pandemic situations like COVID-19 can cause.[8,9] It also increases an individual's ability to actively interact with the deluge of conspiratorial information that spreads faster than a disease.[10-12] According to a review of existing research, people with low health literacy are more susceptible to COVID-19 infection and are more likely to experience depression and fear.[13] As a result, adequate health literacy is critical in dealing with the current COVID-19 situation because it not only allows individuals to use credible health information but also prepares them to adopt preventive behaviors. Several studies focusing on samples from medical and non-medical populations using an online questionnaire were conducted in Asia and North America, according to a review of published literature on health literacy related to COVID-19.[9,13-15] The findings of these studies revealed that both general and medical populations had suboptimal health literacy, which was concerning. Seng et al.[16] emphasized the importance of healthcare policymakers knowing the levels and risk factors of pandemic-related health literacy throughout different populations to formulate optimal communication methods.

Higher levels of health literacy have been linked to less fear and anxiety of COVID-19 among medical students in recent studies and might act as a protective factor because students are better able to navigate the coexisting and infodemic conspiracy theories.[14]

Therefore, in a review study, we decided to examine health literacy among university students during the COVID-19 pandemic. It should also be noted that so far there has been no review on this issue and this is the first time.

METHODS

For this systematic review, we followed the guidelines outlined in the PRISMA Statement (priority reporting items for systematic reviews and meta-analyses).[17] The authors have prepared a review protocol, which can be requested. The following study characteristics were used to determine whether a study was eligible for inclusion in the review: The review included cross-sectional studies (study design) examining the health literacy (outcome) of students in

tertiary education of any age (population) in the COVID-19 pandemic. There were no health-related restrictions. Health literacy and related influencing factors are the outcome variables of interest. Nutbeam's health literacy definition[18,19], as well as common health literacy definitions[7], served as a guiding principle in this regard. In terms of eHealth literacy, Norman and Skinner's[20] definition was a deciding factor. The outcome variables in the studies had to be designated as either primary or secondary outcome variables. Three electronic databases were searched to find studies (PubMed, Scopus, and Google Scholar). On July 15, 2021, the last search was conducted. Additionally, the already qualified studies were reviewed for new pertinent references after the search procedure. The databases were searched using combinations of the following keywords: college; university; adolescents; students; eHealth literacy; health literacy; and COVID-19. This review considered studies published in English. **Table 1** contains the entire search query. Two authors conducted the study selection process (title, abstract, and full text). Also, this study is registered on the OSF (ID: https://osf.io/s8c7q/) website.

A data extraction sheet based on the patient/population, intervention, comparison, and outcomes (PICOS) model was used to extract the desired data. Data items were study-relevant information consisting of the name of the study, corresponding authors, the year of publication, the country, characteristics of participants (e.g., age, gender, study program, and course of studies), the underlying setting (university, college), information on the outcome variables consisting of the theoretical background, the assessment instruments used, and information on the results of the study regarding the health literacy of students and its determinants. The data extraction was always performed independently by at least two authors. Any discrepancies between the authors were resolved through discussion until a consensus was reached.

Table 1. The search strategy of PubMed and Scopus databases.

Search engine	Search strategy	Additional filters
PubMed/Medline	(((health literacy[Title/Abstract]) OR (health literacy[MeSH Terms])) AND ((university students[Title/Abstract]) OR (health students, public[Title/Abstract]) OR (dental students[Title/Astract])OR(health occupations students[Title/Abstract]) OR(medical students[Title/Abstract]) OR (nursing students[Title/Abstract]) OR (premedical students[Title/Abstract]) OR (pharmacy students[Title/Abstract])OR (health students, public[MeSH Terms]) OR (dental students[MeSH Terms]) OR (health occupations students[MeSH Terms]) OR (medical students[MeSH Terms]) OR (nursing students[MeSH Terms]) OR (premedical students[MeSH Terms]) OR (pharmacy students[MeSH Terms])) AND ((covid19[Title/Abstract]) OR (covid19 pandemic[Title/Abstract]) OR(covid19[MeSH Terms])))	English June 9th 2022
Scopus	(health literacy*) AND(university students*OR health students, public* OR dental students*OR health occupations students*OR medical students*OR nursing students* OR premedical students*OR pharmacy students*) AND(COVID-19*OR COVID-19 Pandemics*)	English June 9th 2022
CENTRAL	#1:((health literacy): ti, ab,kw #2: MeSH descriptors : [health literacy] explode all trees #3 (university students): ti, ab,kw OR (health students, public): ti, ab,kw c OR(dental students): ti, ab,kw OR(health occupations students): ti, ab,kw OR(medical students): ti, ab,kw OR(nursing students): ti, ab,kw OR(premedical students): ti, ab,kw OR (pharmacy student)s: ti, ab,kw OR(health students, public): ti, ab,kw OR (dental students): ti, ab,kw OR(health occupations students): ti, ab,kw OR (medical students): ti, ab,kw OR(nursing students): ti, ab,kw OR(premedical student): ti, ab,kw s OR(pharmacy students): ti, ab,kw #4 MeSH descriptors: [students] this term only #5 (covid19) :ti,ab,kw or (covid 19 pandemic) :ti,ab,kw #6 Mesh descriptors [covid19] explode all tree #7 #1 or #2 #8 #3 or#4 #9 #5 or #6 #10 #7 and #8 and #9	English June 10th 2022

The risk of bias in the included studies was evaluated using The JBI Critical Appraisal Checklist For Systematic Reviews AND Research Synthesis (HTTPS://JBI.GLOBAL/CRITICAL-APPRAISAL-TOOLS). The caliber of the studies was evaluated independently by two authors. A second author was consulted in the event of a disagreement, and discussions continued until an agreement was reached. To determine the degree of bias present in specific studies, a scoring system was modified.[17,21] According to this method, studies were classified as having a very low risk of bias if they answered at least 10 of the 11 questions correctly, as having a low risk of bias if they answered 8 or 9 of the 11 questions correctly, as having a moderate risk of bias if they answered 6 or 7 of the 11 questions correctly, and as having a high risk of bias if they answered 5 or fewer questions correctly.

On the principles of data synthesis, narrative synthesis was developed.[22] The studies were first organized into groups according to the PICOS scheme, the data were prepared and put into a common descriptive format, and patterns were discovered alongside the studies. Next, a preliminary synthesis was created, which included initial descriptions of the results of the studies used. The links between and within the studies' data were then looked at. It was determined what constitutes general health literacy, as well as its limitations and practical applications. Additionally, logical explanations for the variations between the research's characteristics and findings were developed.

RESULTS

The search in the databases PubMed, Scopus, and Google Scholar resulted in a total of 960 studies. Out of those,780 duplicates were removed. Out of 180 studies, 64 studies were removed for the irrelevant topic. The remaining 116 results were scanned. Eighty-eight studies

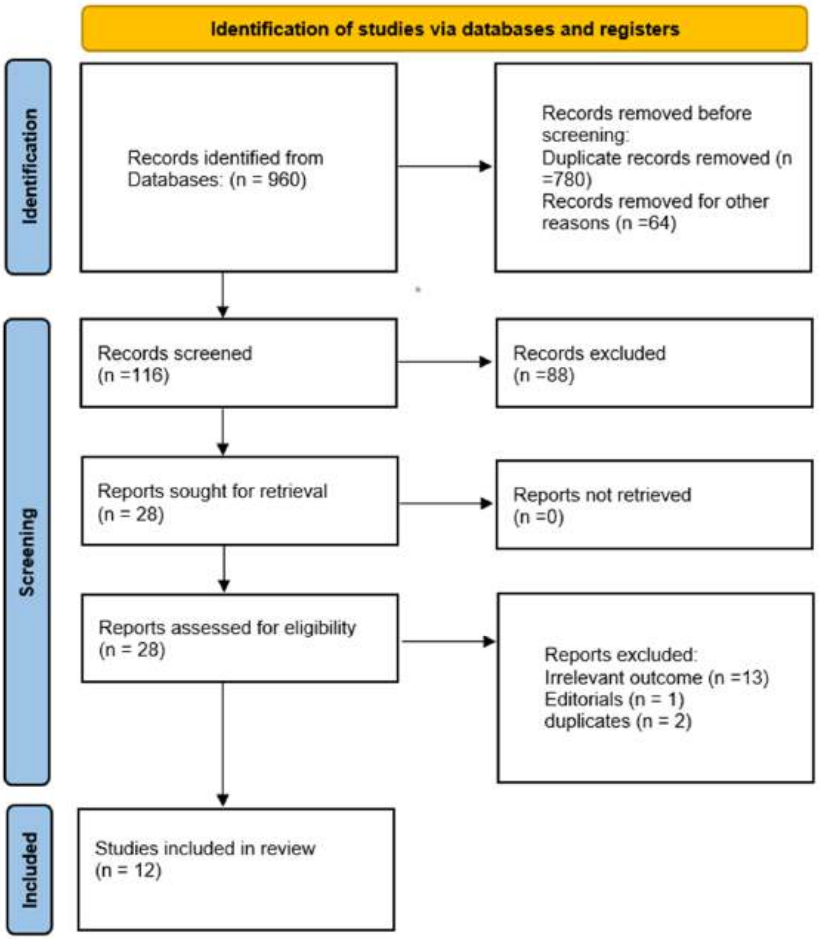

Figure1. PRISMA 2020 flow diagram of the study.

were excluded due to irrelevant topics/abstracts. The full texts of the remaining 28 studies were then reviewed in detail. Thirteen of these did not meet the specified inclusion criteria. Studies that didn't have university students as participants were excluded. Reviews, commentaries, and editorials were excluded. One study was excluded for being an editorial and two studies were removed because of duplicates. Finally, a total of 12 studies were included in the review (**Figure 1**).

Twelve cross-sectional studies investigated health literacy among university students in the COVID-19 pandemic which involved 17773 students. Four studies were performed in Pakistan.[23-26] Two studies were done in Iran.[27,28] The remaining studies were conducted in the USA[29], Vietnam[30], China[31], Colombia[32], Germany[33], and Indonesia[13]. The percentage of female participants ranged from 38.5 to 88.9.

One study included students of One of the 20 health-related degree programs (e.g. nursing, healthcare services, and sciences).[29] Two studies have only medical students as participants. Also, In two studies, most of the participants were studying health-related programs. Seven studies included students from various fields of study.[23-26,32-33,13]

Scales used were HLS-EU (29), HLS-SF12[23,25,26,30], HELIA[28], FCOV-19S[25,28], HLQ (online) (KAP)[24,27,31,13], CHL-p[33], heals[31,33], and pre-validated COVID-19 literacy questionnaire (CLQ) designed by Fauzi et al.

There was a relationship between health literacy and some determinants. Positive determinants included age, female gender, Urban background, cognitive maturity, Higher educational qualification, information source (Health workers), number of semesters, and parental education. Some negative determinants were male gender, rural background, smoking, drinking, being able to pay for medication, lower conspiracy beliefs, and higher fear of COVID-19.

The connection between age and health literacy was shown in seven studies.[24,27,28,30,32-33,13] Better health literacy with increasing age was displayed in five of them.[24,27,10-12] Regarding gender, five studies identified female gender as a positive determinant[23,27,28,31,33] and two studies showed male gender as a negative determinant.[30,33]

Two studies showed a relationship between the course participants were studying and their level of health literacy.[32,33] Two studies suggested that the more mature students were, the better health literacy they had.[29,13]

According to two studies, geographical background played a role in health literacy level, and having an urban background was identified as a positive determinant.[23,26]

DISCUSSION

Among 12 included articles, COVID-19 health literacy was reported as sufficient in 6, insufficient in 3, and not reported in 3. This observation included both health-related and other study fields. Students in health-related fields seem to have higher COVID-19 health literacy. There were several factors introduced to be related to high COVID-19 health literacy; age, female gender, higher educational qualification, parental education, number of semesters, the field of study, source of information, and being from an urban setting. Most of the studies announced that age and number of semesters are positive factors, probably because of increasing cognitive and critical thinking abilities.[34,35] Lower health literacy in rural settings might be associated with limited access to the Internet and a lack of communication channels in these areas. Medical students had higher COVID-19 health literacy scores because they are future doctors and is necessary for them to know more about symptoms, way of transition, diagnosis, treatment, and prevention of disease. Higher health literacy is followed by taking more preventive behaviors and adhering to recommendations.[36,37] Although most students knew the way to search, social media was the most important popular information resource because of its attraction and visualization.[38-41] Information credit is the most determinant of health literacy and the use of social media has a high risk of misinformation.[42,43] One of the abilities of highly health-liberated people is to assess data whether is right or not.[20,44-46] Unfortunately, people with low health literacy have more tendency to trust whatever is said on

social media.

Several factors are said to be relevant to lower COVID-19 fear, including older age, later academic semester, higher educational grades, being male, being single, ability to take medication, and higher health literacy.[47,48] People who had higher fear scores also had unhealthy lifestyles. Moreover, students with higher fear scores tended to smoke or drink to ease their negative emotions temporarily[49-51]; which is in line with several studies indicating that mental disorders and more stressful life status are followed by a higher rate of smoking, substance abuse and dependence.[52,53] Being male was reported to be related to lower fear, possibly because of more stressful life events and higher burdens of duties for women during the pandemic like housework, caregiving, domestic violence, etc.[54-56] Married people are reported to have more fear; one of the main reasons is the fear of infecting their couple and losing their families.[57,58] Although a higher literacy level is associated with lower fear, the results of a study done in Pakistan indicated that health literacy does not predict COVID-19 fear; it might be due to cultural issues and religious beliefs. COVID-19 fear may increase mortality and morbidity rates together with a growing incidence rate of diabetes and heart disease.[59,60] Health literacy was introduced to be a protective factor against depression and anxiety during the pandemic and therefore impacts students' physical and mental health.[61,62]

LIMITATIONS

This systematic review had some limitations. The included articles used different questionnaires with various question levels, so the data were not comparable. Some did not use validated scales and pre-tested questionnaires due to the pressure of time. Those studies that reported higher scores might be in ceiling effect due to easiness of questions. Besides, some of them used online surveys which have the following problems: lack of control over the sample size, selection bias, and the tendency of participating students to be healthy and so possibly of higher health literacy level. Some studies gathered data using a self-report scale which may cause over or lower-estimation of the adherence to recommendations and protocols. Some studies were conducted on limited society, thus they could not be the voice of all (for example, only in one university or only in health-related fields students who might overrepresented in tests). Those articles assessed fear of COVID-19 scales online; thus psychological and mental status of the participants could not truly be evaluated which might affect the final results. As the studies were cross-sectional, we cannot conclude casual relationships between COVID-19 health literacy and the variables investigated. These studies were done in different periods; since the first emergence of covid-19 disease, lots of events occurred including progression in our knowledge of this disease, vaccine production, and mutation formation in the structure of its virus, which influenced our attitude and behavior over time.

IMPLICATION FOR PRACTICE

Health literacy is associated with better health status and plays a protective role against mental and physical health disorders and it reduces carelessness and overreaction.[8,23,62] Additionally, a health-literate society is more likely to adopt health health-protective attitude.[36] There must be an interdisciplinary approach when aiming to promote health literacy. These groups must be prioritized in the plan for COVID-19 health literacy increase: younger students, male gender, lower semester of education, students with low-educated parents from rural settings, and lower grade qualified students. It is not known how exactly the determinants of COVID-19 health literacy interact but it is worthies for policymakers to take into account as many as possible. Universities can conduct online attractive lectures about COVID-19 control and preventive methods for teachers and students. Furthermore, they can implement a competition on the knowledge of this disease to encourage students to learn.

IMPLICATION FOR RESEARCH

There is a need to design an exhaustive questionnaire to examine COVID-19 health literacy. Moreover, extra research is needed to

Table 2. Summary of included studies.

First author (year)	Country	Design	Participants	sex	Theoretical frame(s)	Scaled used	Determinants of health literacy	Quality score	Ref
Vamos et al. (2021)	USA	Cross-Sectional Survey	169 students of one of the 20 health-related degree programs (e.g., nursing, social work, physical therapy, occupational therapy, healthcare services, and sciences) offered by a College of Health and Human Services at a state institution in Michigan was chosen as a sample for research participation.	female (88.9%)	Sørensen et al. [63] Pelikan et al. [64]	HLS-EU	More Mature students [+] Health behaviors: using a hand sanitizer when the water/soap is not available [+] Self-isolation whenever feeling sick or told by a physician [+]	6/8	[29]
Shaukat et al. (2021)	Pakistan	Cross-Sectional Survey	387 students of various fields of social science from the universities of Punjab, Sargodha, and Lahore.	(60.4%) females	Duong et al. [65, 66] Sørensen et al. [67] Liu et al. [68]	HLS-SF12	Geographical background: Urban background [+] Rural background [-]	6/8	[26]
Pourfridoni (2021)	Iran	Cross-Sectional Survey	278 students studying at Jiroft University of Medical Sciences,	192 (69.1%) females	Sánchez et al. [69] Broche-Pérez et al [70]. Nakhostin-Ansari et al. [71] Nemati et al. [72] Barsell et al. [73] Salari et al. [74] Vahedian-Azimi et al. [75]	HELIA FCOV-19S	[+] marital status [+/-] education grade [+] place of residence (rural area) [+] Female gender [-] age	6/8	[28]
Naveed et al. (2022)	Pakistan	Cross-Sectional Survey	249 students of the University of the Punjab, Lahore, the University of Sargodha, Sargodha, and the University of Management and Technology, Lahore in social and business science disciplines.	female (58.6%)	Duong and et al. [65] Sørensen et al. [67]	HLS-SF12	Geographical background: Urban background [+] Rural background [-] Female gender [+]	6/8	[75]

Nguyen et al. (2020)	Vietnam	Cross-Sectional Survey	5423 students at eight universities across Vietnam, including five universities in the North, one university in the Center, and two universities in the South.	(52.1%) females	Spitzer et al. [76]	HLS-SF12	Older age [-] last academic years [-] being men [-] being able to pay for medication [-] smoking [-] drinking [-]	6/8	[14]
Rozeen Shaukat (2021)	Pakistan	Cross-Sectional Survey	271 students of social science and business science disciplines at the Punjab, Lahore, and University of Sargodha, Sargodha.	145 (53.51%) females	Chen et. al. [77] Bierwiaczonek et al. [78] Allington et al. [79] Nguyen et al. [15] Seng et al. [16]	HLS-SF12 FCOV-19S Health Protective Behaviors Conspiracy Beliefs	[+] Higher health protective behavior [-] lower conspiracy beliefs [-] higher fear of Covid-19	6/8	[25]
Fauzi et al. (2020)	Indonesia	Cross-Sectional survey	290 students of the Faculty of Teacher Training and Education in one of the private universities in Malang (biology teacher candidates)	N/A	Maverick Insider [80] Sørensen et al. [7] Mullan et al. [81]	HLQ (online)	Student's year (-), age (+), cognitive maturity (+), information source (Health workers) (+)	6/8	[13]
Faisal et al (2021)	Pakistan	Cross-Sectional survey	353 students from various universities in Pakistan	38.5 % Females	Reuben et al. [83] Azlan et al. [84] (Azlan et al., 2020) (84) Huynh et al. [85] Li et al. [86] Al-Hanawi et al. [87]	HLQ (online) (KAP)	Age (28–38 age group) (+), Education, Study Province	7/8	[82]
Pablo Antonio Archila (2021)	Colombia	Cross-sectional survey	4168 university students in private and state Colombian universities were chosen by convenience sampling	Female (55.2%)	Anju & Arulsamy [88] Hamza et al. [89] [89] (Hamza et al., 2021) Nguyen et al. [90] Seale et al. [91]	Pre-validated COVID-19 literacy questionnaire (CLQ) designed by Fauzi et al.	(+) 21–25-year age group, graduate students (+) graduate students (+) lower than the 2015 year of entry group (+) medical students (-) lower and equal to the 20-year age group (-) undergraduates (-)The 2019–2020 year of entry group (-) arts and humanities students	5/8	[32]

Fazaeli Et al (2021)	Iran	Cross-Sectional Survey	411 students, staff, and faculty in Mashhad University of Medical Science were selected through available sampling as participants	female (65.2%)	Seng et al. [16] Jafari et al. [92] Abel et al. [8] Mntazeri et al. [93] Fazaeli et al. [94] Javadzadeh et al. [95] Patil et al. [96]	HLQ	(+) Higher educational qualification (+) female gender (+) age	6/8	[27]
Heinrichs et al (2021)	Germany	Cross-Sectional Survey	5,021 students at four German universities participated	(69%) females	Tasso et al. [97] Goldstein et al. [98] Margraf et al. [99] Al-Hasan et al. [100](Al-Hasan et al., 2020)(100) Abel et al. [8]	CHL-p wheels	(+) age (+) female gender (+) number of semesters (+)course of studies (+) parental education (+) socioeconomic background (-) male gender (-) frequency of consumption of organic food.	6/8	[33]
Yuehui Jia et al. (2020)	China	Cross-Sectional Survey	753 eligible respondents participated in the survey, among which 740 respondents 561 (75.81%) were medical students, and 179 (24.19%) were nonmedical students. A total of 83 (11.22%) students were from 985 or 211 universities, which are the key universities in China	Female (61.89 [25]%)	Yimenu et al. [101](Yimenu et al., 2020) (101) Al Ahdab et al. [102] Alrasheedy et al. [103] (Alrasheedy et al., 2021) (103)	heals KAP HLQ (online) (KAP)	(+) female gender (+) COVID-19-related KAP among students from key universities in China (+) Good knowledge , attitude and practice among college students	6/8	[31]

+ for promoting determinants
- for inhibiting determinants

determine other potential COVID-19 health literacy determinants and the causal relationships between them and health literacy. Also, future designed interventioMuld be evaluated in the aspect of their effectiveness and cost benefits.

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CONFLICTS OF INTEREST

None.

AVAILABILITY OF DATA AND MATERIAL

The data that support the findings of this study are available from the corresponding author, upon request.

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Identifying Predictors of Mortality in Sepsis Patients with Malignancy: A Retrospective Cohort Study

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ABSTRACT

Background: *Sepsis is a major problem that contributes to a high mortality rate. Its mortality is especially high in patients with malignancy. One study reported that sepsis patients with malignancy have a 2.32 times higher risk of mortality compared to patients without malignancy. For this reason, factors that influence mortality in sepsis patients with malignancy become especially important to provide effective and efficient therapy. This study aims to identify factors that influence mortality in sepsis patients with malignancy.* ***Methods:*** *This study is a retrospective cohort study using medical records of sepsis patients with malignancy who were treated at Cipto Mangunkusumo Hospital from 2020 to 2022. A bivariate analysis was carried out and followed by a logistic regression analysis on variables with p-value<0.25 on the bivariate analysis.* ***Results:*** *Among the 350 eligible sepsis subjects with malignancy, there was an 82% mortality rate (287 subjects). Bivariate and multivariate analyses revealed significant associations between mortality and both SOFA score (adjusted Odds Ratio of 5.833, 95%CI 3.214–10.587) and ECOG performance status (adjusted Odds Ratio of 3.490, 95%CI 1.690–7.208).* ***Conclusion:*** *SOFA score and ECOG performance status are significantly associated with sepsis patient mortality in malignancy cases.*

Keywords: *Sepsis, malignancy, mortality.*

INTRODUCTION

Sepsis is a life-threatening state of organ dysfunction caused by a dysregulation of the patient's body's response to infection. Sepsis can lead to shock, multiorgan failure, and death.[1-3] Globally, sepsis incidence reached 48.9 million cases in 2017, with an associated mortality rate of approximately 11 million cases (22.5%).[4] Unfortunately, specific data for the Indonesian population is currently unavailable. However, data collected from five central hospitals in Indonesia in 2018 reported 14,076 cases of sepsis, with an alarming mortality rate of 8,200 cases (58.3%).[5]

Sepsis patients with malignancy have a more complex pathophysiological process that involves interplay between sepsis and cancer. Furthermore, sepsis patient with malignancy was also reported to have a higher mortality rate compared to those without malignancy. Dager et al.[6] reported that patients with a history of malignancy had a significantly increased risk of mortality, with an odds ratio of 2.326. Similar findings were also observed in studies by Moore et al. and Hajjar et al.[7,8] This difference in complexity and prognosis causes the need for other factors in addition Sequential Organ Failure Assessment (SOFA) score to estimate the mortality of sepsis patients with malignancy.[9]

Several factors potentially contributed to sepsis-related mortality in individuals with malignancies, including age, body mass index, history of chemotherapy, history of radiotherapy, ECOG performance status, SOFA score, cancer stage, neutropenic status, and septic shock.[10-14] Given the multitude of suspected factors and the absence of specific data for the Indonesian population, we aimed to investigate these factors so that they could provide valuable insights for clinical applications.

METHODS

This study was conducted at Cipto Mangunkusumo Hospital, a tertiary care hospital and the national referral center for government hospitals. This study is a retrospective cohort study using sepsis and malignancy patients' medical records from January 2020 to December 2022.

Selection and Characteristics of Included Participants

Sepsis patients with malignancy were included in this study. Sepsis diagnosis was made according to sepsis-3. In patients with insufficient data for calculating the SOFA score, the mSOFA score was used. Meanwhile, malignancy diagnoses were established through the gold standard examination for each type of malignancy with histopathological evidence of malignancy before or during sepsis. The patient's performance status was assessed using Eastern Cooperative Oncology Groups (EGOG) during admission to the hospital ward.

Inclusion criteria in this study include: adult (≥18 years old) patients, sepsis diagnosis was done during admission or hospitalization, sepsis diagnosis was done using gold standard examination while patients with insufficient data were excluded from this study. Medical records of sepsis patients admitted to CiptoMangunkusumo Hospital from December 2020 to December 2022 were first screened for age (≥18 years old) and malignancy. Then, patients without gold standard examinations for malignancy were excluded from this study.

Statistical Analysis

The data obtained was analyzed using SPSS 20.0. Numerical variables were first tested for normality using the *Kolmogorov-Smirnov test*. A normal distribution was defined as a p-value≥0.05. Variables with normal distribution are presented descriptively as mean±SD and are presented as median (min-max) otherwise. Bivariate analysis was performed using either the chi-square test or Fisher's exact test. The variables analyzed were age (<60 years old vs. ≥60 years old), body mass index (<25 kg/m² vs. ≥25 kg/m²), chemotherapy within 28 days, radiotherapy within 28 days, malignancy (solid vs. hematologic), stage of solid tumor (metastasis vs. non-metastasis), SOFA score (≤6 vs. >6), neutropenia, ECOG performance status (0-1 vs. 2-4), and initial sepsis-related shock with mortality as an outcome. Independent variables that show a p-value < 0.25 in the bivariate analysis will proceed to multivariate analysis using logistic regression analysis.

RESULTS

Selection of Subjects

The screening was conducted on sepsis patients who were treated at Cipto Mangunkusumo Hospital between January 2020 and December 2022, using their medical records. Patients aged <18 years and those without cancer were excluded from the study. Additionally, patients lacking a gold standard examination for their respective malignancy diagnoses were also excluded. A total of 350 subjects were included in this study. (**Figure 1**)

Baseline Characteristics of Included Participants

The majority of subjects were women (54.29%) with a median age of 56 years and a body mass index (BMI) of 20.4 kg/m2. Most subjects were in stage IV (69.93%), with a median SOFA score of 7 and a median ECOG score was 3. Fifty-one subjects (14.5%) were treated in the high-care unit. Sepsis occurred after the initiation of treatment in 266 (76%) subjects. The mortality rate was 82%. (**Table 1**).

The lung was the most common source of infection, accounting for 229 cases (65.4%), followed by the urinary system in 42 subjects (12%). Biliary tract infection ranked third, with 41 cases (11.7%), followed by intraabdominal infection in 40 cases (11.4%). Other sources

Table 1. Demographic characteristics of subjects (n=350).

Variables	
Gender	
Male, n(%)	160 (45.71)
Female, n(%)	190 (54.29)
Age (years)*	56 (18-84)
Body Mass Index (kg/m^2)*	20.4 (9.2-37.78)
Stage of solid tumor, n (%)	
I	2 (0.70)
II	8 (2.80)
III	54 (18.88)
IV	200 (69.93)
No data	22 (7.69)
SOFA/mSOFA*	7 (3-17)
ECOG performance status*	3 (1-4)
Intensive or High Care Unit, n (%)	51 (14.5)
Sepsis Intrahospital, n (%)	266 (76)
Blood culture, n (%)	275 (78.6)
Positive Blood culture, n (%)	104 (29.7)
Type of Malignancy, n (%)	
Hepatobiliary dan Pancreas	81 (23.16)
Head and Neck	32 (9.16)
Kidney and urinary system	16 (4.47)
Gastrointestinal	32 (9.12)
Hematological	58 (16.59)
Bone	4 (1.16)
Lung and intrathoracic	12 (3.43)
Thyroid	3 (0.86)
Breast	31 (8.86)
Female Reproduction	59 (16.86)
Others	22(6.29)
Mortality, n (%)	287 (82)

* The data is presented as the mean ± standard deviation (SD) for variables with a normal distribution and as the median (min-max) for variables with a non-normal distribution

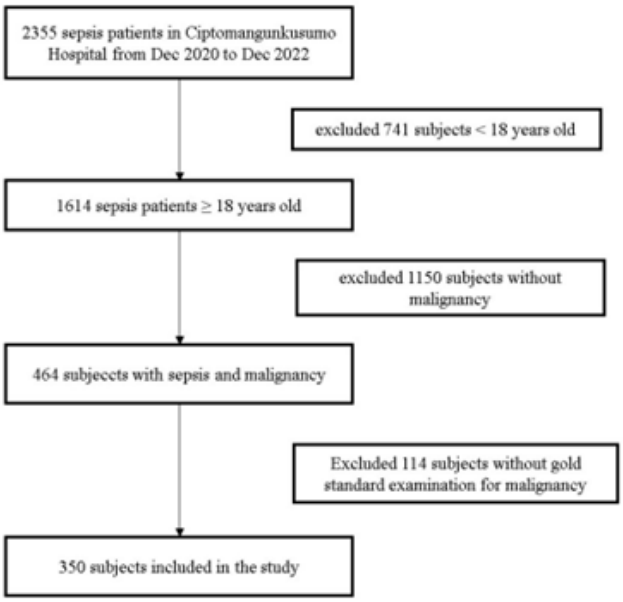

Figure 1. Flowchart of the study.

included skin and soft tissue, neutropenic febrile episodes, catheter-associated bloodstream infections, digestive system infections, ear, nose, and throat infections, and others. (**Table 2**)

Table 2. Infection site.

Infection Site	n (%)
Lung	229 (65.40)
Urinary System	42 (12)
Biliary System	41 (11.7)
Intraabdominal	40 (11.4)
Skin and Soft Tissue	26 (7.40)
Febrile Neutropenia	12 (3.4)
Catheter-Associated Blood Stream Infection	6 (1.7)
Gastroenterology System	6 (1.7)
Head and Neck	2 (0.5)
Others	2 (0.5)

Bivariate Analysis

The bivariate analysis demonstrated statistical significance for both ECOG performance status and SOFA score, with relative risks (RR) of 1.380 (95% CI: 1.096-1.737) for ECOG performance status and 1.492 (95% CI: 1.299-1.714) for SOFA score. (**Table 3**)

Multivariate Analysis

In the multivariate analysis, statistical significance was found for ECOG performance status and SOFA score, with RR values of 1.380 (95% CI: 1.096-1.737) and 1.492 (95% CI: 1.299-1.714), respectively. (**Table 4**)

Table 3. Bivariate analysis.

Variable	Total N (%)	Mortality n (%)	Relative Risk	95% CI	p-value
Age					
< 60 years old	223 (63.71)	176 (78.92)	1.107	1.007-1.217	0.059
≥ 60 years old	127 (36.29)	111 (87.40)			
Body Mass Index					
< 25 kg/m^2	290 (82.86)	235 (81.03)	1.053	0.917-1.210	0.667
≥ 25 kg/m^2	41 (11.71)	35 (85.37)			
Chemotherapy in 28 days					
No	296 (84.57)	248 (83.78)	0.862	0.725-1.025	0.053
Yes	54 (15.43)	39 (72.22)			
Radiotherapy in 28 days					
No	328 (93.71)	268 (81.71)	1.057	0.888-1.258	0.777
Yes	22 (6.29)	19 (86.36)			
Malignancy					
Solid	286 (81.71)	235 (82.17)	0.989	0.869-1.126	0.858
Hematologic	64 (18.29)	52 (81.25)			
Stage of solid tumor					
Non-metastasis	64 (24.24)	49 (76.56)	1.091	0.940-1.266	0.263
Metastasis	200 (75.76)	167 (83.5)			
SOFA Score					
≤ 6	89 (25.43)	53 (59.55)	1.492	1.299-1.714	< 0.001
> 6	261 (74.57)	234 (89.66)			
Neutropenia					
No	311 (88.86)	256 (82.31)	0.966	0.817-1.142	0.660
Yes	39 (11.14)	31 (79.49)			
Performance Status					
0-1	47 (13.43)	29 (61.70)	1.380	1.096-1.737	<0.001
2-4	303 (86.57)	258 (85.15)			
Shock at initial sepsis					
No	161 (46)	127 (78.88)	1.073	0.971-1.186	0.166
Yes	189 (54)	160 (84.66)			

Table 4. Multivariate analysis.

Variables	p-value	Adjusted Odds Ratio	Confidence Interval
Age	0.190	1.564	0.801 – 3.053
Chemotherapy in 28 days	0.470	0.741	0.329-1.671
Shock at initial sepsis	0.315	0.712	0.367 – 1.381
SOFA Score	<0.001	5.833	3.214 – 10.587
ECOG performance status	0.001	3.490	1.690 – 7.208

DISCUSSION

Sepsis patient with malignancy involves an interplay between the two conditions and several other factors (e.g. chemotherapy, invasive procedures, etc.) which causes a more complex process with higher severity.[15] This raised the question of whether the SOFA score can accurately predict mortality in sepsis patients with malignancy as it does not adequately capture the complex interplay of factors displayed in sepsis patients with malignancy. Furthermore, studies have shown that sepsis patients with malignancy have a significantly worse prognosis compared to sepsis patients without malignancy. A meta-analysis by Xiang et al reported a statistically significant increase in mortality in sepsis patients with malignancy compared to sepsis patients without malignancy (OR = 2.46, 95%CI: 1.42-4.25, I2 = 99%).[16]

While the SOFA score has been proven to have a good prognostic value in the general population, its simplistic nature still struggles to adjust to the complexity presented in patients with malignancy. A validation cohort by Greenberg et al. reported prognostic performance of SOFA score in sepsis patients with cancer. In this study, SOFA scores had an Area Under the Curve (AUC) of 0,68 (95%CI: 0.64-0.72) for predicting in-hospital mortality. This prognostic performance is lower compared to when the SOFA score is used in the general population with an AUC of 0.74. Thus, several factors in addition to SOFA score should be considered to more accurately estimate the prognosis of sepsis patients with malignancy. [17,18]

In our study, we evaluated age (<60 years old vs. ≥60 years old), body mass index (<25 kg/m² vs. ≥25 kg/m²), chemotherapy within 28 days, radiotherapy within 28 days, malignancy (solid vs. hematologic), stage of solid tumor (metastasis vs. non-metastasis), neutropenia, ECOG performance status (0-1 vs. 2-4), and initial sepsis-related shock as an additional factors aside from SOFA score (≤6 vs. >6) in patients with malignancy. In the bivariate analysis, we found that age, history of chemotherapy for the last 28 days, shock at the initial diagnosis of sepsis, SOFA score, and ECOG performance status had p-values <0.25. We then performed logistic regression analysis which shows that the SOFA score and ECOG performance status had a significant association with mortality.

We found that SOFA score > 6 is associated with increased mortality in both bivariate and multivariate analysis with p-value<0.001 and adjusted Odds Ratio of 5.833 (95% CI: 3.214 – 10.587). This is to be expected as similar findings have been reported in several previous studies.[19,20] In this study, however, for subjects whose SOFA score cannot be calculated, the SOFA score was replaced using the mSOFA score. This practice is justified by Grissom et al. It was found that the SOFA score and mSOFA score were equally good at predicting mortality.[21]

Patients with ECOG scores 2-4 also have higher mortality compared to patients with ECOG scores 0-1 in this study in both bivariate and multivariate analysis with a value of p = 0.001 and *adjusted Odds Ratio* of 3.490 (95% CI: 1.690 – 7.208). Similar findings were also reported by Torres et al and Rosolem et al in Brazil.[14] This can be attributed to the fact that individuals with poor ECOG performance status often have low organ functional capacity which increases the risk of mortality.[22] Additionally, ECOG performance status reflects overall health and physical condition which also measures how well the body can tolerate the physiological stress during sepsis.

Other variables such as age, stage of cancer, history of chemotherapy, and septic shock were initially suspected of influencing the mortality of sepsis patients with malignancy. However, none

of the variables have statistical significance to mortality. This could be because most patients in these studies have advanced-stage cancer. Only 3.5% were diagnosed with early stages I and II in our study. So, it is likely that the mortality tends to be the same between groups as most patients have poor prognosis to begin with. In the case of the history of chemotherapy, several studies have stated that the effect of chemotherapy on immunosuppression occurs in 7-10 days with a maximum effect observed at 14 days after chemotherapy.[23] This could explain why patients who have completed chemotherapy for more than 14 days may have improved their immunological status and show the same results as those without a history of chemotherapy.

We suggested several differences related to research findings compared with other studies. This may be due to most subjects having advanced malignancy stages and the place of treatment which is a tertiary care hospital and the national referral center for government hospitals. This study illustrated the situation in Indonesia, such as the proportion of cancer cases first diagnosed at the advanced stage (60%), the majority of cancer patients being women and the number of ICUs is low compared to the total population (2.7 per 100,000).[23] For this reason, this study is suitable for describing sepsis patients with malignancy in Indonesia.

Limitation of Study

The drawback of this research is that it uses secondary data. This research was also conducted at one health center only. In addition, several subjects could not be counted on SOFA scores and were replaced with mSOFA.

CONCLUSION

The SOFA score > 6 and ECOG performance status of 2-4 are associated with increased risk of mortality in sepsis patients with malignancy at Cipto Mangunkusumo Hospital.

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Impacts of the COVID-19 Pandemic on the CODE ST-Segment Elevation Myocardial Infarction Program: A Quantitative and Qualitative Analysis

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ABSTRACT

Background: *The CODE ST-segment elevation myocardial infarction (STEMI) program is an operational standard of integrated service for STEMI patients carried out by Dr. Cipto Mangunkusumo Hospital. The emerging coronavirus disease 2019 (COVID-19) outbreak brought about many changes in the management of healthcare services, including the CODE STEMI program. This study aimed to evaluate the healthcare service quality of the CODE STEMI program during the COVID-19 pandemic based on the Donabedian concept.* ***Methods:*** *This was a mixed-methods study using quantitative and qualitative analyses. It was conducted at the Dr. Cipto Mangunkusumo Hospital, a national referral hospital in Indonesia. We compared the data of each patient, including response time, clinical outcomes, length of stay, and cost, from a two-year period between 2018–2020 and 2020–2022 as the pre-COVID-19 CODE STEMI and COVID-19 CODE STEMI periods, respectively. Interviews were conducted to determine the quality of services from the perspectives of stakeholders.* ***Results:*** *A total of 195 patients participated in the study: 120 patients in pre-COVID-19 CODE STEMI and 75 patients in COVID-19 CODE STEMI. Our results showed that there was a significant increase in patient's length of stay during the COVID-19 pandemic (4 days vs. 6 days, $p < 0.001$). Meanwhile, MACE (13% vs. 11%, $p = 0.581$), the in-hospital mortality rate (8% vs. 5%, $p = 0.706$), door-to-wire crossing time (161 min vs. 173 min, $p = 0.065$), door-to-needle time (151 min vs. 143 min $p = 0.953$), and hospitalization cost (3,490 USD vs. 3,700 USD, $p = 0.945$) showed no significant changes. In terms of patient satisfaction, patients found CODE STEMI during COVID-19 to be responsive and excellent.* ***Conclusion:*** *The implementation of the CODE STEMI program during the COVID-19 pandemic revealed that modified pathways were required because of the COVID-19 screening process. According to the Donabedian model, during the pandemic, the CODE STEMI*

program's healthcare service quality decreased because of a reduction in efficacy, effectiveness, efficiency, and optimality. Despite these limitations attributed to the pandemic, the CODE STEMI program was able to provide good services for STEMI patients.

Keywords: *COVID-19, STEMI, CODE STEMI, health care service, Donabedian component.*

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is the most lethal emergency condition of acute coronary syndrome.[1] Immediate reperfusion plays an important role in preventing further damage to the myocardium. It is commonly known that the earlier STEMI is treated, the better the clinical outcome.[2] Regarding the management of STEMI patients, Dr. Cipto Mangunkusumo Hospital has implemented the CODE STEMI program. This program established a collaborative system for treating STEMI by evaluating its management starting from emergency department admission to definitive revascularization. Various benefits of the program have been obtained, both by patients and health care personnel, including improved service quality, reduced major adverse cardiac events (MACEs) and mortality rates, and reduced costs.[3] However, the emergence of coronavirus disease 2019 (COVID-19) brought about many changes in the management of healthcare services, particularly at the beginning of the pandemic.[4,5] Health services must change and modify services, including the CODE STEMI program, to prevent nosocomial transmission. This may have had an influence on the quality of services during that time.

Thus, in this study, we evaluated the healthcare service quality of the CODE STEMI program at Dr. Cipto Mangunkusumo Hospital during the COVID-19 pandemic by using Donabedian's concept.

METHODS

Study Design and Setting

This was a mixed-methods research using quantitative and qualitative methods. It compared the service quality of the CODE STEMI program before and during the COVID-19 pandemic using Donabedian's concept. The quantitative method was adopted by comparing the medical data of CODE STEMI patients before and during the COVID-19 pandemic. The qualitative method was applied through interviews to determine the quality of services from the perspectives of stakeholders. This research was conducted at the National Referral Center General Hospital, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

In 1966, Avedis Donabedian introduced an evaluation method using structure, process, and outcome elements, also known as the SPO model. Then, through the book *Introduction to Quality Assurance in Health Care*, published in 2003, Donabedian explained seven main components that can be used to assess the quality of health services: efficacy, effectiveness, efficiency, optimality, acceptability, legitimacy, and equity.[6] In this study, we used Donabedian's concept to evaluate the impact of the COVID-19 pandemic on the quality of services of the CODE STEMI program.

Study Participants

The research sample was obtained using a total sample technique according to the specified time limit. The participants were STEMI patients undergoing the CODE STEMI program. The CODE STEMI program is designed for STEMI patients who arrive at the hospital < 12 hours after the onset of symptoms. This time frame follows the recommendations of the European Society of Cardiology.[7] The management of the CODE STEMI program primarily consists of fibrinolytic and primary percutaneous coronary intervention (PPCI).

The exclusion criteria included STEMI patients with MACEs as comorbidities at admission and severe comorbidities, which could potentially influence the observed variables. Major adverse cardiac events at hospital

admission were defined as patients with STEMI presenting with stroke, acute decompensated heart failure, lethal arrhythmia, cardiac tamponade, pericarditis, cardiogenic shock, and death. Severe comorbidities included acute stroke, liver cirrhosis, chronic inflammation, sepsis, autoimmune disorders, and malignancies. In addition, patients with incomplete medical record data were excluded from the study.

The participants were divided into two groups: the pre-pandemic period group (September 15, 2018 to March 15, 2020) and the pandemic period group (March 16, 2020 to December 31, 2022). The duration of the pre-pandemic and pandemic periods was based on the day that the Indonesian government declared COVID-19 a national disaster in Indonesia.

The interview participants were determined using a purposive sampling approach to obtain the perspectives and experiences of health workers and patients. Six informants were interviewed in this study.

Assessment of Variables

We collected data on the basic characteristics of the CODE STEMI patients, including gender, age, cardiovascular risk factors, and CODE STEMI treatment options. The evaluation variables included categorical variables, such as clinical outcomes (MACEs and mortality), and numerical variables, such as door-to-needle time, door-to-balloon time, length of stay, and costs.

We collected data on the basic characteristics of the interview participants, including gender, age, education, and occupation. The data obtained from the interviews were processed based on the context of Donabedian's evaluation components. Each informant was asked different questions regarding their role in the program.

Data Analysis

The data were analyzed using the Stata program version 15.1. We compared the patient baseline characteristics and the assessment variables before and during the COVID-19 period. Chi-square and Mann–Whitney tests were used to analyze categorical and numerical variables, respectively. The interview data were grouped into structure, process, and outcome components. We used the triangulation method to confirm the validity of the information obtained.

Ethical Consideration

This research followed the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, under number KET-883/UN2.F1/ETIK/PPM.00.02/2021.

RESULTS

Quantitative Analysis

A total of 195 patients met the inclusion criteria, with 120 STEMI patients who underwent the CODE STEMI program before the COVID-19 pandemic and 75 STEMI patients who underwent the CODE STEMI program during the COVID-19 pandemic. **Table 1** presents the baseline patient characteristics of both groups, including gender, age, cardiovascular risk factors, and CODE STEMI treatment choices. The proportions of gender and age between the groups were found to be similar. There was a significant increase in hypertension as a cardiovascular risk factor in the pandemic period (54% vs. 79%, $p = 0.035$). Other cardiovascular risk factors showed no significant differences. In this study, fibrinolytic percentage was found to be significantly increased (3% vs. 16%, $p = 0.002$) along with a significant decrease in PPCI percentage (97% vs. 84%, $p = 0.002$).

During hospitalization, the clinical outcomes between the two groups showed no statistical significance for in-hospital MACE (13% vs. 11%, $p = 0.581$) and in-hospital mortality rate (7% vs. 5%, $p = 0.706$) (**Table 2**). The result for response time showed no statistically significant differences in door-to-wire crossing time (161 min vs. 173 min, $p = 0.065$) and door-to-needle time (151 min vs. 143 min $p = 0.953$). Hospitalization cost also showed no statistically significant difference (3,490 USD vs. 3,700 USD, $p = 0.945$). Meanwhile, the length of stay was significantly longer during the COVID-19 pandemic (4 days vs. 6 days, $p < 0.001$) (**Table 3**).

Qualitative Analysis

The qualitative method was carried out through interviews to determine the quality of services from the perspectives of stakeholders. **Table 4** shows the characteristics of the informants.

Table 1. CODE STEMI patients' baseline characteristics.

Characteristics	Pre-COVID-19 CODE STEMI (n = 120)	COVID-19 CODE STEMI (n = 75)	*p*-value
Gender - n (%)			
Male	102 (85)	64 (85)	0.949
Female	18 (15)	11 (15)	
Age - median (range)	53 (48-61)	55 (48–61)	0.670
Risk factors n (%)			
Diabetes	55 (46)	32 (43)	0.665
Hypertension	65 (54)	52 (79)	0.035*
Dyslipidemia	43 (36)	30 (40)	0.559
Obesity	13 (10.8)	7 (9.3)	0.737
Acute Kidney Injury	22 (18)	15 (20)	0.773
Chronic Kidney Disease	12 (10)	9 (12)	0.661
CODE STEMI treatment - n (%)			
Primary PCI	116 (97)	63 (84)	0.002*
Fibrinolytic	4 (3)	12 (16)	0.002*

Values are median (range) or n (%).
PCI = percutaneous coronary intervention
*Significant difference.

Table 2. Comparison of clinical outcomes in CODE STEMI patients before and during the COVID-19 pandemic.

Variables	Pre-COVID-19 CODE STEMI (n = 120)	COVID-19 CODE STEMI (n = 75)	p-value
In-hospital MACE - n (%)			
Yes	16 (13)	8 (11)	0.581
No	104 (87)	67 (89)	
In-hospital mortality - n (%)			
Yes	8 (7)	4 (5)	0.706
No	112 (93)	71 (95)	

Values are means ± SDs, medians (IQR), or n (%).
MACE = Major adverse coronary event.

Table 3. Comparison of response time, length of stay, and cost in CODE STEMI patients before and during the COVID-19 pandemic.

Variables	Pre-COVID-19 CODE STEMI (n = 120)	COVID-19 CODE STEMI (n = 75)	*p*-value
Door-to-needle time (min)	151 (64-226)	143 (77-219)	0.953
Door-to-wire crossing time (min)	161 (131-220)	173 (148-238)	0.065
Length of stay (days)	4 (4-6)	6 (5-7)	<0.001*
Cost (USD)	3,490 (3,160 – 4,550)	3,700 (3,100 –5,400)	0.945

Values are means ± SDs, medians (IQR), or n (%).
*Significant difference.

Table 4. Demographic characteristics of the informants.

Number of the informant	Sex	Age	Education	Job
1	Male	50	Cardiology specialist	Physician
2	Male	39	Emergency medicine specialist	Physician
3	Female	42	Bachelor's	Nurse
4	Female	39	Bachelor's	Nurse
5	Male			Patient
6	Male			Patient

The structural components of the CODE STEMI program can be categorized into policy and operational preparedness, facility, and providers. The interview with the informants suggested that the CODE STEMI program had a good preparation in terms of policy:

Participant 1: "*There were policy changes to adjust to pandemic conditions and to avoid transmission between fellow patients and health workers."*

Participant 3: *"During the pandemic, there was a change in the flow of the CODE STEMI program, which required COVID-19 examination (i.e., polymerase chain reaction [PCR]); patients with onset of chest pain < 12 h without contraindications to fibrinolytic agents and confirmed to have COVID-19 were suggested to have fibrinolytic first."*

In terms of facilities, several obstacles were encountered during the implementation of the CODE STEMI program during the pandemic, especially during its early days, when additional tools, such as PCR tests and swabs, were still very limited, and it took days for test results to come out. In addition, the supply of personal protective equipment (PPE) was still limited, and the cardiac catheterization room was not yet negatively pressured to facilitate infectious patients.

Participant 1: "*At the beginning of the pandemic, there were difficulties in handling STEMI patients with suspected COVID-19 because they had to wait for the PCR results, which took a very long time. Alternatively, according to the guidelines of the Dr. Cipto Mangunkusumo Hospital, patients were administered thrombolytics and temporarily isolated.*"

Participant 2: "*The relatively high shortage of PPE, especially at the beginning of the pandemic, was due to people still adapting to the pandemic.*"

Participant 4: "*At the beginning of the pandemic, there were limitations to patients' life support equipment.*"

In terms of human resources, health workers were limited in the emergency department, while there was no lack of human resources in the cardiac ward.

Participant 3: "*There has never been a lack of human resources during the pandemic, especially during periods of high COVID-19 cases.*"

Participant 4: "*There were limited human resources in the emergency room, especially when there were confirmed COVID-19 patients.*"

During the COVID-19 pandemic, there were several plans in place, such as work-from-home arrangements:

Participant 1: "*The health status of medical workers remained a priority by implementing work from home, especially for the elderly.*"

The process component consisted of communication, the availability of drugs, and documentation. Based on the interviews that were conducted, communication during the COVID-19 pandemic was one of the informants' concerns:

Participant 1: "*Improving communication and coordination among health workers is important for better outcomes.*"

Participant 2: "*Getting an adequate history and physical examination, including difficulties obtaining an electrocardiogram examination, was challenging during the pandemic.*"

Most patients and their families have low to middle education levels, so some patients, especially at the beginning of the pandemic, were still in denial about COVID-19:

Participant 1: "*Patient and family responses at the beginning of the pandemic were mostly denials, but over time, after a lot of information, they understood.*"

Participant 2: "*When a patient passed away because of suspected COVID-19, the family did not accept it; there was denial, particularly when the body of the patient was treated differently.*"

Participant 3: "*Because of clinical and radiological similarities between COVID-19 and STEMI, especially in the complication stage (i.e., myocarditis and pulmonary edema), patients and families did not accept if the test results were positive for COVID-19.*"

Through a change in policy in the administration of fibrinolytic, drug availability and accessibility were ensured:

Participant 2: *"For cardiac therapy, there were no difficulties with device and drug availability."*

Participant 4: *"There are no drug limitations,*

including fibrinolytic agents."

An aspect that was improved during the pandemic was the data recording process. Enhanced electronic-based recording was successfully implemented to reduce the risk of infection exposure:

Participant 1: "*Recording and documentation were accelerated through electronic medical records [EMRs]. Communication was accelerated through online platforms.*"

The outcome component consisted of the patient's clinical outcomes and satisfaction levels. Based on the interviews conducted, one informant said that the condition of a patient was worsened by the presence of COVID-19 infection.

Participant 4: "*During the COVID-19 pandemic, the condition of a STEMI patient was exacerbated by a positive COVID-19 diagnosis."*

From the perspective of patient satisfaction, it was found that the patients felt that the CODE STEMI program during COVID-19 was responsive and provided good service.

Participant 5: "*Based on my experience as a patient, pandemic conditions did not complicate patient care. The services provided by the ER were swift. I did not have to wait for a long time. The medical staff who served me were very helpful and provided quite comprehensive information. The funding was done using National Health Insurance, so there were no additional costs that needed to be paid by patients."*

Participant 6: "*In my experience as a patient, the services provided were good. Nothing was difficult when I arrived in the ER. At that time, the ER was very full and chaotic, but I realized that all procedures had to be carried out to determine whether a patient had COVID-19. In my opinion, additional examinations, such as the PCR swab, are necessary. I'm not bothered by that."*

DISCUSSION

The CODE STEMI program at the Dr. Cipto Mangunkusumo Hospital has been in operation since 2017 and is constantly being improved. In previous studies, we evaluated the service quality of the CODE STEMI program by demonstrating numerous benefits from both clinical and managerial aspects.[3] Nonetheless, many changes in the CODE STEMI program during the COVID-19 pandemic could have made an impact on service quality. **Figure 1** illustrates the changes in the algorithm before and during the COVID-19 pandemic.

In this study, fewer patients met the inclusion criteria for the CODE STEMI program in the pandemic period compared to the pre-pandemic period (120 vs. 75, $p = 0.949$). This could be due to a decrease in the total number of patients who visited the Dr. Cipto Mangunkusumo Hospital during the COVID-19 pandemic. The same conditions were also experienced in various health centers during the COVID-19 pandemic worldwide.[8–11] Limited access because

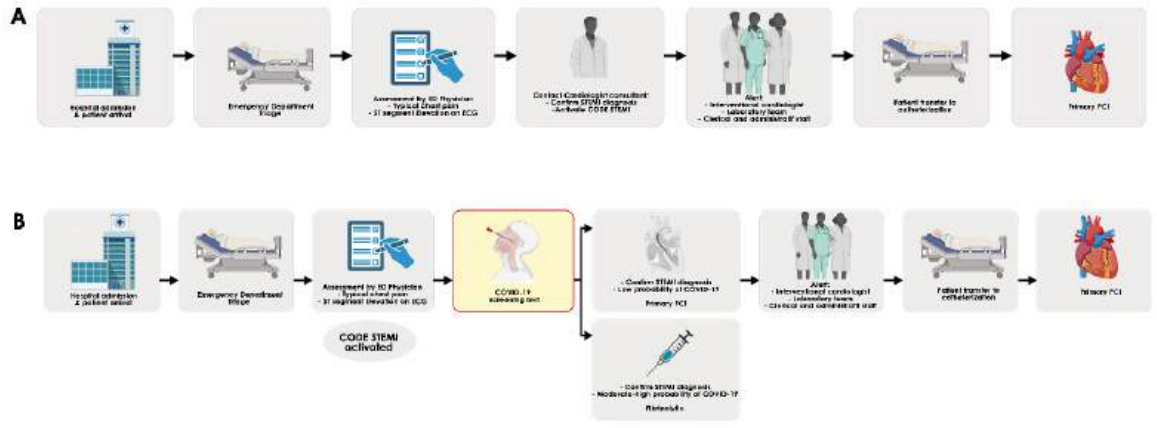

Figure 1. Illustration of the algorithm of the CODE STEMI program before the COVID-19 pandemic (A) and during the COVID-19 pandemic (B). Created with Biorender.com premium license by Eka Ginanjar.

of lockdowns and the fear of being exposed to the virus contributed to the decrease in hospital admission rates of STEMI patients.[12,13] In addition, the CODE STEMI program is intended for STEMI patients with a symptoms-to-hospital duration < 12 h; thus, this condition is difficult to achieve because the symptoms-to-hospital time in STEMI patients during the pandemic was reported to be prolonged.[14,15] As a result, patients with prolonged time are unable to enter the CODE STEMI program algorithm.

During the pandemic, PPCI remained the main recommendation for treating patients with STEMI. Primary percutaneous coronary intervention is associated with better outcomes in patients with STEMI compared with thrombolysis. Following World Health Organization guidelines, all health workers in catheterization labs are required to wear appropriate PPE.[16] The American Heart Association recommends a negative pressure lab specialized for patients with positive COVID-19 results.[17] However, as the informant stated, the availability of PPE was limited. In addition, providing a negative pressure catheterization lab was not possible because of hospital conditions. With these considerations, thrombolytics were prioritized as the initial drugs for STEMI patients without thrombolytic contraindications.[16] According to this study, there was an increase in the percentage of procedures administering thrombolytics during the COVID-19 pandemic (3% vs. 16%, $p = 0.002$).

We observed some variable components, which included response time (i.e., door-to-wire crossing time) and clinical outcomes (i.e., MACEs and mortality), that can be considered components of efficacy and effectiveness. According to our findings, there was an increased door-to-wire crossing time during the COVID-19 pandemic, but this was not statistically significant (161 vs. 173, $p = 0.065$). This condition may have occurred because of the influence of the addition of COVID-19 screening procedures as part of the CODE STEMI algorithm. The CODE STEMI algorithm during the pandemic recommends that STEMI patients with a symptoms-to-hospital duration < 12 h and a probability of being infected with COVID-19 be prioritized for fibrinolytic as long as there are no contraindications, while patients must be confirmed negative for COVID-19, preferably for PPCI. The screening system for COVID-19 status for the patients included medical history, physical examination, chest X-ray, PCR test, and laboratory tests. Especially at the beginning of the pandemic, the availability of PCR equipment was very limited, and the process took quite a long time. This resulted in delays in patient treatment. Delayed reperfusion, especially PPCI, was also experienced in various countries around the world, such as China, England, France, the Netherlands, and Pakistan.[14,18–21] This delay in response time may have affected MACEs and mortality. These rates were more likely to increase during the COVID-19 pandemic compared to the pre-COVID-19 CODE STEMI period. Thus, it may indicate that there was a reduction in the efficacy and effectiveness of the CODE STEMI program during the COVID-19 pandemic.

To evaluate efficiency, we can refer to the amount of healthcare service benefits and the costs of these healthcare services. The benefits of health care services can be observed by assessing MACEs, mortality, and length of stay. Our study found no statistically significant differences in clinical outcomes, such as in MACEs (13% vs. 11%, $p = 0.581$) and mortality (7% vs. 5%, $p = 0.706$). However, there was a significant prolonged duration of the length of stay, indicating a reduction in benefits. The inadequate laboratory capacity for PCR in Indonesia at the beginning of the pandemic led to delays in diagnosing COVID-19 and performing reperfusion therapy.[22] This delay also contributed to a greater incidence of MACEs and mortality, a longer length of stay, and greater costs. This increased length of stay during the COVID-19 pandemic was also experienced in various countries, such as China and India.[23,24] Therefore, based on the results of the data analysis, the efficiency of healthcare services in the CODE STEMI program was reduced during the COVID-19 pandemic.

The optimality component can be evaluated by comparing the obtained profit and the costs expended. A program can be said to be optimal

if it has achieved maximum effectiveness at a low cost. In this study, we found that during the COVID-19 pandemic, the CODE STEMI program experienced reduced effectiveness and increased costs. Therefore, it can be said that it was less than optimal at the time.

Physical distancing was implemented to prevent the transmission of COVID-19 infection. However, physical distancing had a negative impact on communication during the pandemic. As the informants stated, communication problems occurred not only between health care staff but also between health care staff and the patients/families themselves. Our results are similar to those of other studies in that the use of telehealth entailed several limitations, including the inability to effectively assess and treat patients.[25] Nevertheless, there was innovation in the use of EMRs. This research highlights the benefits of EMRs in helping prevent the transmission of COVID-19. The use of EMRs is known to have various benefits, such as facilitating easy access to patient health information that is considered accurate and reliable by health care providers.[26]

Acceptability is defined as conformity to the wishes, desires, and expectations of patients and their families, while equity is defined as conformity to a principle that determines what is just and fair in the distribution of health care and its benefits among members of the population.[6] Despite the inevitable delays in treatment because of mandatory infection control procedures and changes in reperfusion strategies during the outbreak, the patients believed that medical personnel handled their tasks properly and efficiently. The patients stated that there were no management issues as a result of the COVID-19 pandemic.

Legitimacy is defined as conformity to social preferences, as expressed in ethical principles, values, norms, mores, laws, and regulations.[6] Changes in the CODE STEMI program were made based on international recommendations and guidelines, which were adapted to local conditions.

Limitations

This was a single-center study, and the data were specific, as they were obtained from a single institution. The small number of samples included in the study may have affected the results. Thus, increasing the number of samples and extending the time covered in the sampling technique can be considered in future research to obtain better results.

CONCLUSION

The implementation of the CODE STEMI program during the COVID-19 pandemic revealed that modified pathways are required because of the COVID-19 screening process. According to Donabedian, during the pandemic, the CODE STEMI program's healthcare service quality decreased because of a reduction in efficacy, effectiveness, efficiency, and optimality. Despite these limitations brought about by the pandemic, the CODE STEMI program was able to provide good services for STEMI patients.

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Validation of Drug Resistance in Pneumonia (DRIP) Score as Empirical Antibiotic Failure Predictor in Community-Acquired Pneumonia Patients in Cipto Mangunkusumo Hospital

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ABSTRACT

Background: *The incidence of CAP due to Drug-Resistant Pathogen (DRP) requires broad-spectrum antibiotic therapy, Drugs Resistance in Pneumonia (DRIP) score can predict these cases. The use of the DRIP score can prevent antibiotic failure and long hospitalization, but validation is needed so that the DRIP score can be used according to the local community at Cipto Mangunkusumo National Central Public Hospital.* ***Methods:*** *This research is a retrospective cohort study in CAP patients who were hospitalized during the period January 2019 to June 2020. Data were taken from medical records. Failure of empiric antibiotics occurs when one of these criteria is found: patient mortality, ICU transfer, and escalation of antibiotics as well as length of stay.* ***Results:*** *480 patients met the criteria. There were 331 patients (69%) with a DRIP score of <4 and 149 patients (31%) with a DRIP score of≥4. A total of 283 patients (59%) of antibiotic failures were detailed in 174 patients with a DRIP score <4 and 109 patients DRIP score ≥4. DRIP calibration using the Hosmer-Lemeshow test obtained p-value= 0.667 (p>0.05). AUC observations on the ROC curve obtained 0.651 (95% CI; 0.601-0.700).* ***Conclusion:*** *The DRIP score has low accuracy performance and calibration value in predicting empirical antibiotic failure and poor discriminatory value.*

Keywords: *DRIP score, antibiotics failure, Drug-Resistant Pathogens, Community-Acquired Pneumonia.*

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the major causes of mortality and morbidity in the world impacting substantial health and economic[1]. CAP is still commonly found in Indonesia with an incident rate of 1.8% while in Jakarta with an incidence of 2.4% which exceeds the national rate.[2] The bacterial pathogens causing CAP vary according to the characteristics and geographic location of the host, rapid identification and recognition of CAP, can improve outcomes and reduce the risk of death.[3]

The use of appropriate antibiotics becomes a very important preventive and curative effort for successfully resolving MDR (Multidrug Resistance) and interventions against the complexity of resistance, at least slowing the rate of MDR occurrence.[4] In recent years, several cases of CAP have been associated with the emergence of Drug-Resistant Pathogens (DRP). DRP requires different antibiotic therapy compared to the empiric antibiotics recommended in the CAP therapy guidelines. Against DRP pathogens, the initial empirical antibiotics given include antipseudomonal and anti-MRSA. A large number of risk factors associated with DRP have been identified by research worldwide, currently classified into four categories: (1) Pathogen acquisition, (2) Persistent colonization, (3) selective pressure on resistant organisms, and (4) Invasion lower respiratory tract.[5]

The Drug Resistance in Pneumonia (DRIP) score was published in the United States in 2016 by Webb as a predictive model with the most external validation compared to other prediction methods. The study shows that the DRIP score has better predictive accuracy compared to several other alternative scoring systems. The DRIP score is composed of ten risk factors associated with DRP pathogens, including history of antibiotic use, length of hospital stays, enteral nutrition, history of DRP pathogen infection with previous, history of previous medication, chronic lung disease, poor functional status, gastric acid suppression, wound care, and history of MRSA colonization.[5] In recent study in Jakarta showed that the DRIP score had good predictions for assessing drug-resistant pathogens in CAP, patient characteristics, and patterns of bacteria in RSUPN Dr. Cipto Mangunkusumo Jakarta.[6]

There is a need for new and better methods to predict drug-resistant antibiotics while restricting unnecessary widespread use of antibiotics.[7] The decreased use of broad-spectrum empiric antimicrobials will increase by 9% if using the DRIP score.[8] In the pneumonia population with an increase in the prevalence of CAP-DRP, inadequate initial antibiotic therapy is associated with poor outcomes, including death. Overtreatment with antibiotics is preferable for inadequate empiric therapy given the poor outcome evidence. Additional studies are needed to guide the safe and timely de-escalation of antibiotics in patients with antibiotic cultures at moderate to high risk of CAP-DRP.

We hypothesized that the accuracy of the DRIP score as a predictor of failure of empiric therapy and length of stay of CAP patients treated at RSUPN Dr. Cipto Mangunkusumo.

METHODS

The study was a retrospective cohort design that was performed at Cipto Mangunkusumo National Central Hospital, Jakarta, Indonesia by the review ethics review committee University of Indonesia Medical Faculty (Number: KET-1250/UN2.F1/ETIK/PPM.00.02/2022), data collection was done from November to December 2022 by tracing the medical records of community-acquired pneumonia patients who were hospitalized from January 2019 to June 2020. The consecutive sampling method was used and the inclusion criteria included: 1) CAP patients who were hospitalized; 2) Age ≥18 years; 3) Administer empirical antibiotics when the patient is admitted to the hospital. Data were excluded if there was a history of administration of meropenem antibiotics and incomplete data. DRIP score variable data or risk factors were collected from medical records with a score <4 included in the low-risk group and a score ≥4 included in the high-risk group. The definition of empiric antibiotic failure is determined when one of the following variables is found: 1) antibiotic escalation; 2) transfer to the ICU; or 3) patient' mortality. Quantitative data were analyzed with SPSS version 22.

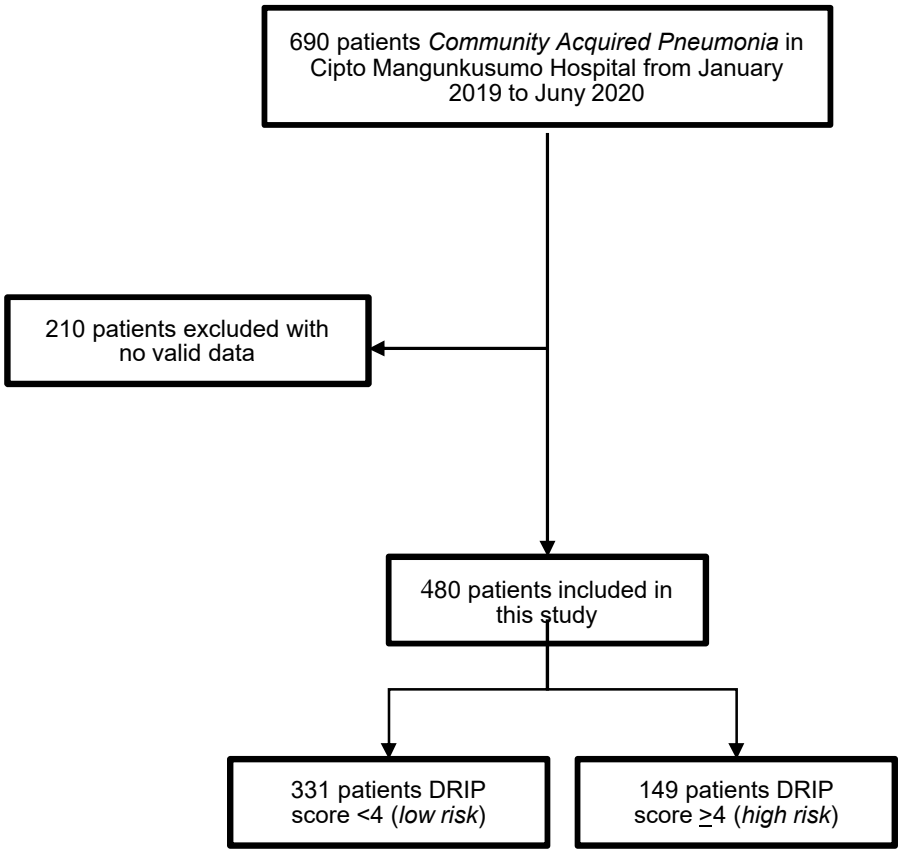

Figure 1.

RESULTS

There are 480 patients included as research subjects. Overall, most patients were in the 18–60-year age group, as well as in the DRIP score group <4; but in the DRIP score group ≥4 more in the age group> 60 years. There were more males than females, both in the DRIP score <4 (low risk) and DRIP score ≥4 (high risk).

Diabetes mellitus is the most common comorbid (27.1%) found in both groups. Poor functional status was found in all study subjects (100%), this happened because all hospitalized patients were considered to have poor functional status according to this study's operational definition. There was no data found for MRSA colonization in all study subjects. The most common risk factor was a history of gastric acid suppression (36.5%), followed by enteral nutrition (25.1%) and a history of hospitalization (17.1%). Risk factors for previous history of infection with drug-resistant pathogens (DRP), were only found in 11 patients (2.3%) who had previous treatment data at RSCM and had culture examination results.

In **Table 2** of the empiric antibiotic failure factor, it was found that of the 141 people who experienced mortality, 90 people (63.8%) had a DRIP score <4, while the remaining 51 people (36.2%) had a DRIP score ≥4. From **Table 2** can be seen that the length of stay of all community pneumonia patients in both groups had a median value of 9 days, quartile 1 was at 6 days and quartile 3 was at 16 days. The high-risk group had a median value of 9 days with quartile 1 at 5 days and quartile 2 at 16 days.

Table 3 shows that the failure of empiric antibiotics in community-acquired pneumonia patients is more than the success of empiric antibiotics, as many as 283 patients (59.0%) experienced empiric antibiotic failure. In the DRIP score <4 group, the proportion of failure (52.5%) was higher than the success of empiric antibiotics (47.5%). In the DRIP score group ≥ 4 it was found that there were more failures (73.2%) than successes of empiric antibiotics therapy (26.8%).

Table 1. Characteristics of high and low-risk patients with community-acquired pneumonia.

Characteristic	n=480 (%)	DRIP Score	
		<4 n= 331 (%)	≥4 n= 149 (%)
Demographic cireteria			
Age(years), median (IQR)	59 (47.89-59)	58 (46-68)	61 (51.5-70.78)
Age, n (%)			
18-60 year	257 (53.5)	185 (55.9)	72 (48.3)
>60 year	223 (46.5)	146 (44.1)	77 (51.7)
Gender, n (%)			
Men	256 (53.3)	175 (52.9)	81 (54.4)
Women	224 (46.7)	156 (47.1)	68 (45.6)
Comorbidities, n(%)			
Diabetes Melitus	130 (27.1)	89 (26.9)	41 (27.5)
Malignancy, n (%)	120 (25)	76 (23)	44 (29.5)
Chronic Kidney Disease, n (%)	108 (22.5)	71 (21.5)	37 (24.8)
Cerebrovascular Disease, n (%)	84 (17.5)	46 (13.9)	38 (25.5)
Congestive Heart Failure, n (%)	75 (15.6)	54 (16.3)	21 (14.1)
Chronic Liver Disease, n (%)	34 (7.1)	19 (5.7)	15 (10.1)
Chronic Lung Disease, n (%)	27 (5.6)	13 (3.9)	14 (9.4)
DRP Risk Factor in DRIP Score			
Antibiotic use within 60 days			
0	416 (86.8)	322 (97.6)	94 (63.1)
2	63 (13.2)	8 (2.4)	55 (36.9)
Long-term care resident			
0	407 (84.8)	324 (97.9)	83 (55.7)
2	73 (15.2)	7 (2.1)	66 (44.3)
Tube feeding			
0	359 (74.9)	276 (83.6)	83 (55.7)
2	120 (25.1)	54 (16.4)	66 (44.3)
Drug-resistant pathogens pneumonia within a year			
0	467 (97.7)	328 (99.4)	139 (93.9)
1	2 (0.4)	1 (0.3)	1 (0.7)
2	9 (1.9)	1 (0.3)	8 (5.4)
Hospitalization within 60 days			
0	398 (82.9)	312 (94.3)	86 (57.7)
1	82 (17.1)	19 (5.7)	63 (42.3)
Chronic pulmonary disease			
0	455 (94.5)	320 (96.7)	135 (90.6)
1	25 (5.2)	11 (3.3)	14 (9.4)
Poor function status			
0	0 (0)	0 (0)	0 (0)
1	480 (100)	331 (100)	149 (100)
Gastric Acid Suppression Use			
0	305 (63.5)	244 (73.7)	61 (40.9)
1	175 (36.5)	87 (26.3)	88 (59.1)
Active wound care			
0	440 (91.7)	314 (94.9)	126 (84.6)
1	40 (8.3)	17 (5.1)	23 (15.4)
MRSA colonization within one year			
0	480 (100)	331 (100)	149 (100)
1	0 (0)	0 (0)	(0)

Table 2. Empiric antibiotic failure factors.

Outcome	Total	DRIP Score	
		<4	≥4
Antibiotik escalation, n (%)			
No	262 (54.6)	201 (60.7)	61 (40.9)
Yes	218 (45.4)	130 (39.3)	88 (59.1)
Transferred to ICU, n (%)			
No	449 (93.5)	306 (92.4)	143 (96)
Yes	31 (6.5)	25 (7.6)	6 (4)
Mortality, n (%)			
No	339 (70.6)	241 (72.8)	98 (65.8)
Yes	141 (29.4)	90 (27.2)	51 (34.2)
Length of stay (days), Median (IQR)	9 (6-16)	10 (6-16)	9 (5-16)

Table 3. Empiric antibiotics failure on DRIP score.

Outcomes	Total	DRIP Score	
		<4	≥4
Empiric Antibiotic Therapy			
Success	197 (41.0)	157 (47.4)	40 (26.8)
Failure	283 (59.0)	(2.6)	109 (73.2)

The DRIP score performance is determined from the calibration and discrimination values. In this study, the calibration of the Drug Resistance in Pneumonia Score (DRIP) as a predictor of empirical antibiotic therapy failure can be assessed by comparing the two expected and observed groups. In the Hosmer-Lemeshow test, p=0.667 where the DRIP score has a good calibration based on the statistical significance of the Hosmer-Lemeshow test (p>0.05).

Discrimination ability The DRIP score has an AUC (area under the curve) value on the ROC curve obtained: AUC 0.651 (95% CI; 0.601-0.700). The AUC value of 0.6-0.7 indicates that the DRIP score has a poor discriminatory value in predicting failure of empiric antibiotic therapy (transfer to ICU, antibiotic escalation, and mortality) in CAP patients. At a cut-off value of ≥ 4, the DRIP score can differentiate between high and low-risk groups with a sensitivity value of 38.52%, a specificity of 79.70%, a positive predictive value of 73.15, a negative predictive value of 47.43, a positive likelihood ratio of 1.9, and negative likelihood ratio 0.77.

Table 4. DRIP Score Calibration in Expected and Observed Groups (n=480).

		Empiric Antibiotic Failure	
Score	N	Observed	Expected
1	2	1	0.738
2	147	61	66.229
3	90	53	48.153
4	92	59	56.817
5	82	55	56.895
6	67	54	54.168

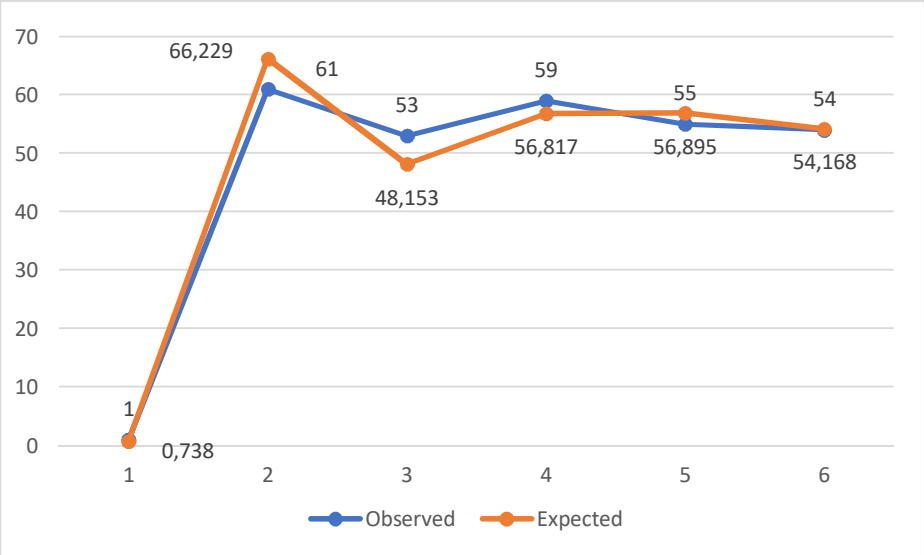

Figure 1. Graphic of DRIP Score Calibration in the Expected and Observed Groups.

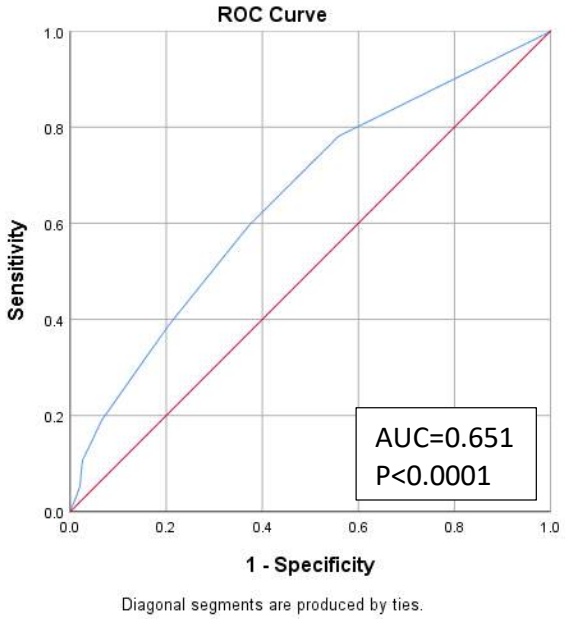

Figure 2. ROC Curve of DRIP Score Validation.

In **Table 5** the distribution of the data of length of stay CAP patients treated at Cipto Mangunkusumo Hospital Jakarta were skewed. The relationship test with data that was not normally distributed was carried out using the Mann-Whitney test. Length of stay of CAP patients treated in Cipto Mangunkusumo General Hospital was not related to DRIP (p=0.483).

Table 5. Mann Whitney Test DRIP Score with Length of Treatment.

Variable	Skor DRIP		p Value
	Low Risk	High Risk	
Length of Stay, Median (IQR)	9 (6-16)	9 (5-16)	0.438

DISCUSSION

In this study, although not much different, the incidence rate of CAP was higher in males compared to females. This can happen due to men's smoking habit in the region. In the age category, the number of respondents aged 18-60 years was 53.5%, not too far off and almost comparable to those aged over 60 years which reached 46.5%. Older age is a risk factor for CAP in the community, where they will have more risks which make them susceptible to CAP and have a much worse prognostic tendency compared to a younger age.[9]

Most of the empirical antibiotics used were dominated by non-pseudomonal antibiotics. Previous study stated that the actual use of ceftriaxone alone has the same effective effect compared to the combination of azithromycin in treating CAP. The appropriate choice of initial antibiotic for community-acquired pneumonia patients in the low-risk class (DRIP score <4) is a combination of Ceftriaxone and Azithromycin, while for high-risk (DRIP score ≥4) the use of β-lactam anti pseudomonas antibiotic combined with vancomycin and azithromycin are more recommended.[10]

Antibiotic escalation in the DRIP score <4 groups was performed on 48.1% of respondents, while in the DRIP score ≥4 groups it was performed on 59.1% of respondents. The study stated that the possibility of determining the escalation of antibiotics was carried out by considering the clinical conditions and comorbid factors present in the patient when the treatment was carried out.

In this study the low-risk group has more transfers to the ICU than the high-risk group, it is possible that this data was caused by an unequal number between the DRIP score group <4 and the DRIP score group ≥4. We assume that because the DRIP score indicator does not show the transfer of community pneumonia patients to the ICU, the DRIP score is not quite accurate in seeing and predicting the occurrence of the transfer of patients to the ICU.

This study found that 141 people died with 90 (63.8%) of them having a DRIP score <4, while 51 (36.2%) had a DRIP score ≥4. The findings of this study indicate that the low-risk group has more mortality than the high-risk group. This is compatible with Babbel's study (2018) which showed that only 3 patients (7%) in the hospital mortality category had a high risk of infection due to drug-resistant pathogens in community pneumonia. We assume that this is due to the severity of CAP and the patient's comorbidities at the time of admission to the ER.

Length of stay of all CAP patients in both groups with a mean of 12 days and a median of 9 days, with an interquartile of 6 days to 16 days. The high-risk group had a median of 9 days with an interquartile of 5 days to 16 days. This is compatible with a previous study with a mean length of stay of 11.5 days and a median of 9 days with an interval of 7 days to 14 days.[11]

As far as the authors know, this is the first study in Indonesia to examine the validation of the DRIP score associated with empirical antibiotic failure and the length of stay of CAP patients. This validation test is very important to do before it is used in the clinical practice of health services, considering that there will be differences in patient characteristics. This research is a retrospective study by taking medical record data, so there is an information bias factor. Some of the limitations of this study are incomplete data related to the DRIP score variable in medical records such as previous MRSA colonization.

Assessment of internal validity is carried out by paying attention to whether the sample obtained (actual study subjects) can represent the desired sample according to the selection criteria (intended sample). The validity of this selection was assessed from the sampling method and predetermined selection criteria, both inclusion and exclusion. The sampling method in this study as a whole was carried out consecutively, which is the best sampling method for the category of non-probability sampling. In this study, 480 subjects were successfully recruited. On this basis, the internal validity of this study was considered quite good.

CONCLUSION

A study has been conducted to determine the accuracy of the DRIP score in CAP patients at Cipto Mangunkusumo National Central Hospital.

The DRIP score has low accuracy performance and calibration value in predicting empirical antibiotic failure and poor discriminatory value.

CONFLICT OF INTEREST

No potential conflict of interest in this study

ACKNOWLEDGMENTS

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The Association between Anemia and Mortality of Severe Pneumonia COVID-19 Patients in the High Care Unit of a Tertiary Hospital in Jakarta

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ABSTRACT

Background: *Numerous studies explored the association between anemia and mortality in patients with severe pneumonia due to COVID-19. However, the findings were inconsistent. Therefore, this study was conducted to investigate the association between anemia at HCU admission and in-hospital mortality in severe pneumonia COVID-19 patients.* ***Methods:*** *This retrospective cohort study obtained data on 110 COVID-19 patients with severe pneumonia who were admitted to the HCU between January, 1st 2021, and May 31st, 2021. Patients were categorized as anemic and non-anemic based on the World Health Organization (WHO) guidelines. The demographic and clinical characteristics of the subjects were described. The Chi-squared test was carried out followed by a logistic regression test to determine the association of anemia and mortality.* ***Results:*** *Anemia was observed in 31% of 110 patients with severe pneumonia COVID-19. The source population consisted of 60.9% men and 39.1% women with a median age of 58 years. The most prevalent comorbidity was hypertension (38.2%), followed by diabetes mellitus (27.2%), renal diseases (19.1%) and heart diseases (10%). TAnemia on HCU admission was associated with in-hospital mortality in patients with severe pneumonia COVID-19 (RR: 2.794, 95% CI 1.470-5.312). After adjusting comorbidities as confounding factors, anemia was independently associated with mortality (RR: 2.204, 95% CI: 1.124-4.323, P < 0.021). The result also showed anemic patients had longer lengths of stay and higher levels of D-dimer than non-anemic patients. The median duration length of stay among the anemic and non-anemic was 16 (11-22) and 13 (9-17) days, respectively. The median D-dimer among the anemic and non-anemic was 2220 µg/ml and 1010 µg/ml, respectively.* ***Conclusion:*** *There is a significant association between anemia at HCU admission and mortality in patients with severe pneumonia COVID-19 during hospitalization.*

Keywords: *Anemia, Mortality, Severe Pneumonia COVID-19, Retrospective Cohort.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a recently emerged novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which has rapidly become a global health concern.[1] The most common symptoms at onset include fever, fatigue, dry cough, myalgia, and dyspnea. While headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are less common symptoms.[2] Most of COVID-19 patients have mild symptoms. According to Shang Y et al., there were 14% of patients developed into severe cases, and 5% became critically ill with a mortality rate of 2.3-3.83% mortality.[3] Patients with mild symptoms are treated at home and self-isolated, while those who suffer from severe pneumonia and are critically ill require hospitalization or admitted to the intensive care unit.[4] Severe cases are diagnosed by SpO_2 less than 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) less than 300 mm Hg, respiratory rate more than 30 breaths/min, and/ or lung infiltrates more than 50%. Patients with respiratory failure, septic shock, and/or multiple organ dysfunction are categorized as critically ill.[5]

Anemia is defined by WHO as hemoglobin (Hb) levels less than 12.0 g/dL in women, and less than 13.0 g/dL in men. The low level of hemoglobin describes a condition where the number of red blood cells and their oxygen-carrying capacity are insufficient to meet the body's physiologic needs.[6] Hemoglobin acts as a carrier of oxygen (O_2) in the lungs and releases it to various tissue organs. Hemoglobin also plays an important role in maintaining blood oxygen balance and partial pressure (PaO2) levels. Specific physiology varies in every individual, and the most common cause of anemia is nutritional deficiencies. Other causes include acute and chronic inflammation, parasitic infections, as well as inherited or acquired disorders affecting hemoglobin synthesis.[6,7]

Pneumonia in COVID-19 causes lung injury, leading to a decline in the oxygen levels resulting in a decline of oxygen level in the blood, which makes the oxygen supply to tissues become limited. Low Hb levels reduce the ability of blood to deliver oxygen, thereby worsening the disease. As a result, anemia is deemed to increase mortality in severe pneumonia COVID-19.[7]

Previous studies investigated the association between anemia and COVID-19, but the results were inconsistent. Several studies in various countries reported that COVID-19 patients with anemia are at higher risk of developing severe pneumonia infection and higher risk of mortality.[8,9] However, this finding contradicts the findings of a study in Italy, which found that anemia often occurs in the viral infection but is not directly associated with mortality.[3] Cecconi, et al. also reported that there was no significant association between Hb levels and survival of COVID-19 patients.[10] Therefore, this study aimed to determine the association between anemia and mortality of patients with severe pneumonia COVID-19 who were treated at the HCU of the tertiary facility, Dr. Cipto Mangunkusumo General Hospital, which serves as a national referral hospital in Jakarta, Indonesia. Even though right now COVID-19 is not a pandemic disease anymore, as clinicians we will meet COVID-19 as sporadic cases in clinical practice.

METHODS

A retrospective cohort study was conducted on all patients diagnosed with severe pneumonia and COVID-19 who met the eligibility criteria. at HCU KIARA Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia between January 1st, 2021, and May 31st, 2021 We enrolled 110 COVID-19 patients with severe pneumonia who were admitted high care unit at the hospital. We categorized the patients into two groups based on their Hb levels on admission. Anemia was defined based on WHO guidelines where normal levels for men and women are >13g/dL and >12g/dL, respectively.

This study collected data from electronic medical records (EHR) using the total sample method, which was subsequently reviewed by the Department of Internal Medicine at the study site. which were then analyzed by the Department of Internal Medicine at the study site. This study protocol was reviewed and approved by the ethical committee in the Faculty of Medicine

Universitas Indonesia, approval number KET-667/UN2.F1/ETIK/PPM.00.02/2022. The inclusion criteria were patients over the age of 18, who were admitted to HCU Kiara, underwent a laboratory examination including Hb levels, and positive results of Polymerase Chain Reaction (PCR) swab examination. The exclusion criterion is no data on the date of death.

The demographic and characteristics of patients' data variables are presented in either frequency and percentage or median and interquartile range. Statistical analysis was carried out with Chi-square to determine the association between anemia and in-hospital mortality followed by logistic regression to adjust the confounding factors. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Mac version 26.0 tool. P-values of < 0.05 were regarded as statistically significant.

RESULTS

A total of 34 out of 110 patients with severe pneumonia COVID-19 who were admitted to HCU at the study hospital were anemic, accounting for 31% of the sample population.

The study participants were categorized into two groups for comparison based on the Hb cut-off, as shown in **Table 1** and **2**. **Table 1** shows the demographic and clinical characteristics of the patients with a median age of 58 years (interquartile range 47.75-66). The samples consisted of 67 (60.9 %) men and 43 (39.1 %) women. The most common comorbidity in this study was hypertension (38.2%), followed by diabetes mellitus (27.3 %) renal disease (19.1%), and heart disease (10 %).

Patients with anemia on admission had a higher length of stay, with a median duration of 16 (11-22) days in anemic patients and 13 (9-17) days for non-anemic patients, respectively.

Table 2 describes the laboratory findings of severe pneumonia COVID-19 patients. The total median Hb was 13.7 with a range of 12.0-14.8, while non-anemic and anemic patients had values of 14.4 and 10.7, respectively. Furthermore, all of the samples demonstrated high CRP levels, where the non-anemic and anemic groups had 93.0 and 61.1, respectively with a median of 80.7 mg/dl. At the time of admission, the median D-dimer of 110 patients was 1220 µg/ml, with non-anemic patients having values of 1010g/ml and anemic patients having values of 2220g/ml.

Table 1. The Demographic and Clinical Characteristics of Study Participants.

Patients' Characteristic	Total (n=110)	Non-anemia (n=76)	Anemia (n=34)
Age, *(median, IQR)*	58 (47.75-66)	58 (51-65.75)	57.50 (34.75-68.50)
Gender			
Male *n, (%)*	67 (60.9)	45 (59.2)	22 (64.7)
Female *n, (%)*	43 (39.1)	31 (40.8)	12 (35.3)
Comorbidity			
Hypertension *n, (%)*	42 (38.2)	30 (39.5)	12 (35.3)
Diabetes Mellitus *n, (%)*	30 (27.3)	24 (31.6)	6 (17.6)
Renal Disease *n, (%)*	21 (19.1)	15 (19.7)	6 (17.6)
Heart Disease *n, (%)*	11 (10)	4 (5.3)	7 (20.6)
Others *n, (%)*	39 (35.5)	27 (35.5)	12 (35.3)
No Comorbidity *n, (%)*	1 (0.9)	1 (1.3)	
Length of stay *(median, IQR)*	14 (10-18)	13 (9-17)	16 (11-22)
Initial Oxygen Therapy *n, %*			
Nasal Cannula	13 (11.8)	6 (7.9)	7 (20.6)
Simple mask	13 (11.8)	8 (10.5)	5 (14.7)
Non-rebreathing mask	31 (28.2)	22 (28.9)	9 (26.5)
Non-invasive ventilation	49 (44.5)	36 (47.4)	13 (38.2)
Intubation	4 (3.6)	4 (5.3)	
Antiviral therapy			
Remdesivir, *n (%)*	78 (70.9)	57 (75)	21 (61.8)
Favipiravir, *n (%)*	9 (8.2)	7 (9.2)	2 (5.9)
Oseltamivir,n (%)	7 (6.4)	4 (5.3)	3 (8.8)
No antiviral therapy, n (%)	16 (14.5)	8 (10.5)	8 (23.5)

Table 2. Laboratory findings of severe pneumonia COVID-19 patients in the HCU

Laboratory Findings	Total (n=110)	Non-anemia (n=76)	Anemia (n=34)
Haemoglobin(median,IQR)	13.7 (12.0-14.8)	14.4 (13.7-15.40)	10.7 (8.53-11.9)
White blood cells (median, IQR)	9085 (6355-12162)	8760 (6057-10727)	10730 (6417-13375)
Trombosit (median,IQR)	227500 (169750-284250)	225000 (171000-267000)	239500 (157500-308750)
CRP (median, mg/dl, IQR)	80.7 (35.525-149.100)	93.0 (40.300-161.525)	61.1 (13.125-116.700)
D-Dimer (median, µg/ml, IQR)	1220 (565-2777.50)	1010 (480-1965)	2220 (847.5-3825)

The results found that 15 out of 34 (44.1%) anemic inpatients died. **Table 3** shows that anemia is a significant risk factor for death due to severe pneumonia in COVID-19 patients. Furthermore, there was a significant association between anemia and mortality during hospitalization of severe pneumonia COVID-19 patients in men and women (RR: 2.794, 95% CI 1.470-5.312, p = 0.001).

We performed logistic regression analysis to adjust the results of bivariate analysis by adding confounding variables, and we established an independent association between anemia on HCU admission and in-hospital mortality in COVID-19 patients with severe pneumonia, that were hypertension, diabetes mellitus, kidney disease, heart disease using regression analysis anemia was independently had an association with mortality (RR: 2.204, 95% CI: 1.124-4.323, p = 0.021).

DISCUSSION

We found that anemia on HCU admission in patients with severe pneumonia COVID-19 is independently associated with a higher risk of in-hospital mortality. This condition has been observed in critically ill patients, but knowledge regarding its relationship with the viral infection is still lacking.[11] This study was carried out among 110 severe COVID-19 inpatients treated at the HCU with a median age of 58 years (IQR: 47.75-66 years), of which 60.9% and 39.1% were men and women, respectively. A total of 34 anemic and 76 non-anemic inpatients were found, namely 31% and 69% of the population, respectively.

Furthermore, more than half of the patients had more than one comorbidity, with hypertension being the most common in 38.2%, followed by diabetes mellitus, kidney disease, and heart disease in 27.3%, 19.1%, and 10%, respectively.

Table 3. The bivariate analysis between anemia and in-hospital mortality in patients with severe pneumonia COVID-19.

Anemia Status	Alive n, %	Dead n, %	RR (CI 95%)	p
Non-anemia	64 (84.2)	12 (15.8)	2.794 (1.470-5.312)	0.001
Anemia	19 (55.9)	15 (44.1)		

Table 4. The logistic regression analysis of anemia and mortality, as adjusted by confounding variables.

	RR (CI 95%)	p
Crude RR : Anemia	2.794 (1.470-5.312)	0.001
Adjusted		
+ Hypertension	2.654 (1.406-5.009)	0.003
+ Diabetes Mellitus	2.539 (1.329-4.854)	0.005
+ Kidney Disease	2.356 (1.201-4.621)	0.013
+ Heart	2.427 (1.248-4.724)	0.009
+ Others	2.204 (1.124-4.323)	0.021

This finding is consistent with Tao, et al. where these conditions were comorbid for severe pneumonia COVID19.[8] Starke, et al. carried out a meta-analysis of seventy studies, which showed that increasing age as well as comorbidities were related to disease severity, but the mechanism was still unclear.[12]

Patients with anemia on admission had a longer length of stay. This study also assessed anemic or non-anemic patients based on their Hb levels using the WHO guidelines, with a median duration of hospitalization of 16 (11-22) days and 13 (9-17) days, respectively. This finding is in line with a study conducted by Mi Oh, et al., which reported that patients with anemia on admission had a longer duration.[11]

Coagulation disorders, such as disseminated intravascular coagulation (DIC), are often found in severe COVID-19 infections. Anemia was associated with coagulation variables because anemic patients have higher D-dimer levers compared to others.[13] Based on a study in Wuhan, China, the condition was an independent risk factor associated with severe COVID-19, and CRP as well as D-dimer levels were significantly higher in affected people.[8] Furthermore, D-dimer is a fibrin degradation product, which is often used to diagnose thrombosis disorder, and its levels at admission increase along with the severity of community-acquired pneumonia (CAP).[14] The majority of patients in this study had high levels above 500 g/ml, with medians of 1010 g/ml and 2220 g/ml in the non-anemic and anemic groups, respectively. These results are consistent with findings of the study conducted by Helin, et al., which showed that anemic patients had higher levels of D-dimer.[13]

Anemia is common among severely ill patients due to inflammation, and it has been reported to aggravate the severity of the underlying disease and is related to poor outcomes as well as mortality in COVID-19 patients. Previous studies also revealed that it can worsen with age and the presence of comorbidities.[8] In another observational study among 206 patients, anemia was a common manifestation of COVID-19 but had no direct association with mortality.[15] In this study, a statistically significant association was found between the condition of anemia and death during hospitalization of patients with severe pneumonia COVID-19 (P = 0.001). This finding is consistent with Zhou, et al., which also obtained a similar significant association (P = 0.0094). Furthermore, this is in line with another study in Iran where the frequency of death, ICU admission, and need for ventilators were significantly higher in anemic patients compared to others.[9] Most of the COVID-19 infections associated with anemia are caused by an inflammatory process, which is characterized by elevated or normal serum ferritin. In the majority of cases, it is also indicated by decreased transferrin saturation as well as increased inflammatory indicators, such as erythrocyte sedimentation rate (ESR) and CRP .[15]

CONCLUSION

The proportion of anemia in patients with severe pneumonia COVID-19 in the HCU was 31%. Furthermore, 15 of 34 anemic patients died during hospitalization, and they accounted for 44.1% of the sample population. This study found a significant association between anemia on HCU admission and in-hospital mortality in COVID-19 patients with severe pneumonia. As a clinician, if we find sporadic severe COVID-19 patients in the HCU who experience anemia, then the clinician should correct the Hb level immediately to the normal range.

DATA AVAILABILITY STATEMENT

The data used to support the findings are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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Gaucher Disease: A First Reported Adult Case in Indonesia

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ABSTRACT

A 44-year-old female presented with a distended abdomen and fatigue. On physical examination, prominent splenomegaly was found. The laboratory investigations revealed pancytopenia and decreased albumin-globulin ratio. The abdominal ultrasonography revealed splenomegaly, cholelithiasis, and cystitis, and the bone survey showed osteopenia. Differential diagnoses included leukemia, multiple myeloma, and myelofibrosis therefore bone marrow puncture was performed. However, histopathologic examination found Gaucher-like cells in the bone marrow aspiration. The finding of CD68 positivity in Gaucher-like cells by using the immunohistochemistry staining supporting Gaucher disease. To confirm the diagnosis, an examination of glucocerebroside substrate from the patient's blood plasma was performed. Glucosylsphingosine, a deacylated form of glucosylceramide, was markedly elevated. Therefore, the diagnosis of Gaucher disease was confirmed. This is the first reported adult Gaucher case diagnosed in Indonesia.

***Keywords**: Gaucher Disease, Splenomegaly, Pancytopenia.*

INTRODUCTION

Gaucher disease (GD) is a lysosomal storage disease that is caused by autosomal recessive mutation in the gene glucocerebrosidase 1 (GBA1), located on chromosome 1q21.[1] This gene GBA1 mutation results in the absence or deficiency of β-glucocerebrosidase, thus leading to progressive accumulation of glucosylceramide within macrophage lysosome resulting cellular and tissue damage.[2]

Gaucher Disease (GD) is a rare genetic disorder with a prevalence is approximately 1 per 40,000-50,000 individuals in the general population.[3] The most common type of Gaucher disease is type I. It has variable onset and affects mainly visceral organs such as the liver, spleen, bone marrow, and occasionally the lung and central nervous system. There are also acute neuropathic (type II) and chronic neuropathic (type III) GD variants, with worse

clinical features and commonly manifested in early infancy or childhood.[4] The novelty of this case report is the first reported case in Indonesia with the finding of Gaucher-like cells in bone marrow biopsy and enzymatic analysis.

CASE ILLUSTRATION

A 44-year-old female came to the hematology medical oncology outpatient clinic with a chief complaint of abdominal distention for the past 3 years. The patient felt uncomfortable in the left upper abdomen and fatigued, despite still being able to perform daily activities. Other complaints were multiple rashes and bruising in her lower extremities. There was no fever, diarrhea, recurrent stomatitis, joint or bone pain. The patient also complained of weight loss of 3 kilograms during the past 3 years. The patient had no complaints about micturition and passing stool. The patient had no history of hypertension, diabetes, asthma, and allergy. There was no family history of hematology disease or similar symptoms. The patient has 3 children and works as a housewife.

The physical examination showed normal vital signs. The patient was 49 kg and 151 cm tall, with a body mass index of 21.49 kg/m^2. There was no jaundiced sclera, strabismus, or abnormal extraocular movement. Both lung and heart examinations showed no remarkable finding. The abdominal inspection showed a distended abdomen but no sign of abdominal varices or caput medusa. Liver palpation revealed an enlargement of 10 cm below the costal margin, and 6 cm below the xiphoid process. The spleen was Schuffner VII (**Figure 1**). There were no ascites. Another finding was multiple bruising in the lower extremities. There was no palpable lymph node in the neck, axilla, and inguinal.

The laboratory examination showed pancytopenia (Hb 9 g/dL, Hct 28%, WBC 3,010/μL, Platelet 20,000/μL). The reticulocyte count was 138%, and the corrected reticulocyte was 0.61. The lactate dehydrogenase was 219. There was no evidence of hepatitis B, Hepatitis C, and HIV infection. Peripheral blood smear showed normocytic normochromic, anisopoikilocytosis, fragmentocyte, and ovalocyte. In addition, white blood cell examination showed normal cell count and morphology. Platelet examination revealed normal morphology, but with decreased cell count. Other results were hyperferritinemia 1,904.6 ng/mL and increased globulin 3.9 g/dL, with low serum albumin level (3.6 g/dL).

Abdominal ultrasonography found cholelithiasis, cystitis, severe splenomegaly with craniocaudal diameter size was 28.9 cm and no sign of portal hypertension.

Differential diagnoses included chronic myeloid leukemia, multiple myeloma, and myelofibrosis. Then bone marrow biopsy was performed as there was pancytopenia, showing normocellular bone marrow tissue, normal maturation of the myeloid series, and

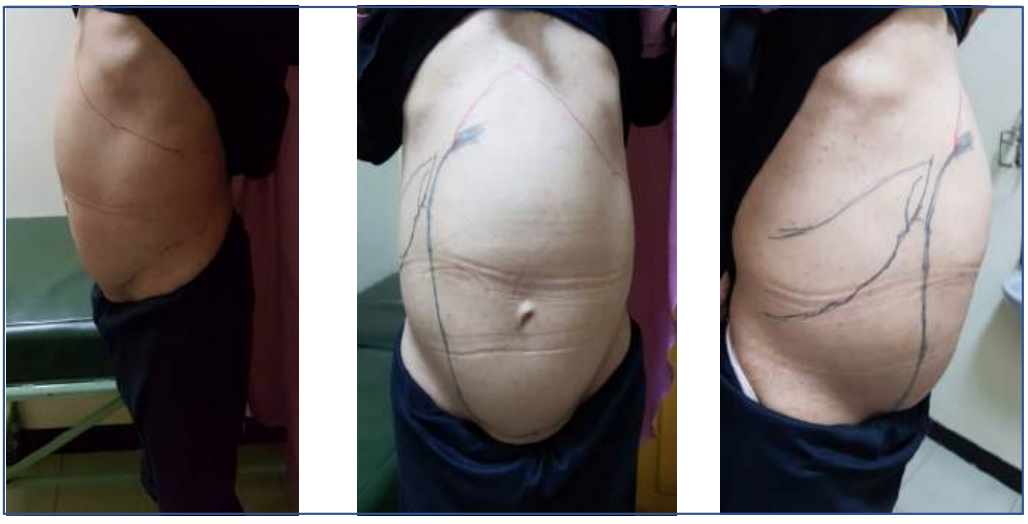

Figure 1. Splenomegaly Schaffner VII.

normal megakaryocyte morphology. Several clusters of histiocytes were found. The cells have small nuclei and the cytoplasms showed a "folded tissue paper" appearance, resembling Gaucher cells. No fibrosis was apparent (**Figure 2**). Based on bone marrow biopsy results, the diagnosis leads to Gaucher-like disease and can rule out other differential diagnosis such as leukemia, multiple myeloma, and primary myelofibrosis. For further diagnostic purposes, immunohistochemistry staining and JAK2 examination were proposed.

Immunostaining from the previous bone marrow biopsy specimen was performed. CD20 was found to be positive on small scattered lymphocytes and CD3 was positive on small scattered lymphocyte cells. Ki-67 was positive in 5% of cells and CD68 was positive in the resemblance of Gaucher cells. CD138 was positive on the scattered plasma cells and kappa--lambda ratio was normal (polyclonal). AE 1/AE 3 was negative. Glycophorin A was positive on erythroid lineage (**Figure 3**). The acid-fast bacilli staining was also performed, but the result was negative. Finally, the JAK2 molecular examination showed no V617F mutation in the JAK2 gene. The V617F mutation in the JAK2 gene was done to make sure there were no myeloproliferative neoplasms.

After the bone marrow biopsy was done, the bone survey examination revealed no Erlenmeyer flask deformity, signs of osteopenia, and decreased bone density with rough trabecula.

Diagnosis of GD could be confirmed with the absence or deficiency of β-glucosidase or excessive accumulation of glucosylceramide substrate. The enzyme analysis showed a slightly low β-glucosidase 1.05 uM/hr (normal >1.8 uM/hr; National Taiwan University). Thus, enzyme test was further evaluated and revealed markedly elevated glucosyl sphingosine (Lyso-GL1), 348.5 ng/mL (normal <3.0 ng/mL).

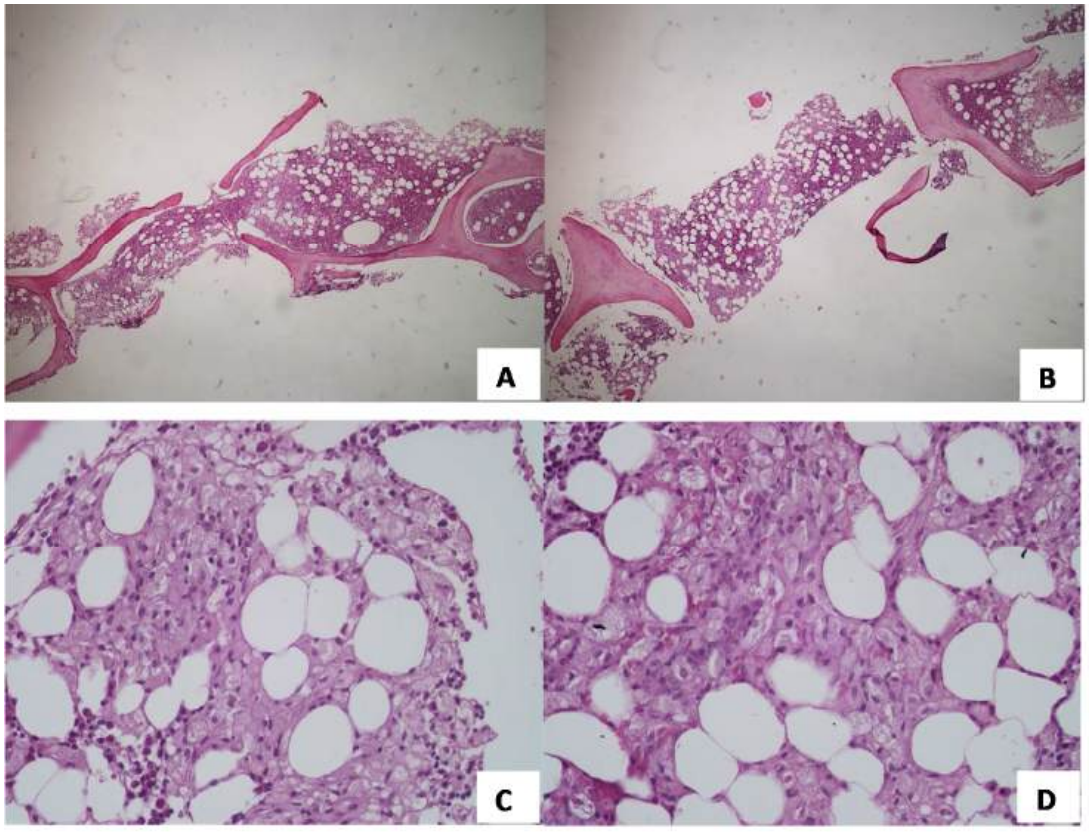

Figure 2. Histopathological features. (A, B) The bone marrow is normocellular, H&E 40x. (C, D) There are some clusters of histiocytes with small nuclei and the cytoplasms show a "folded tissue paper" appearance, resembling the Gaucher cells, H&E 400x.

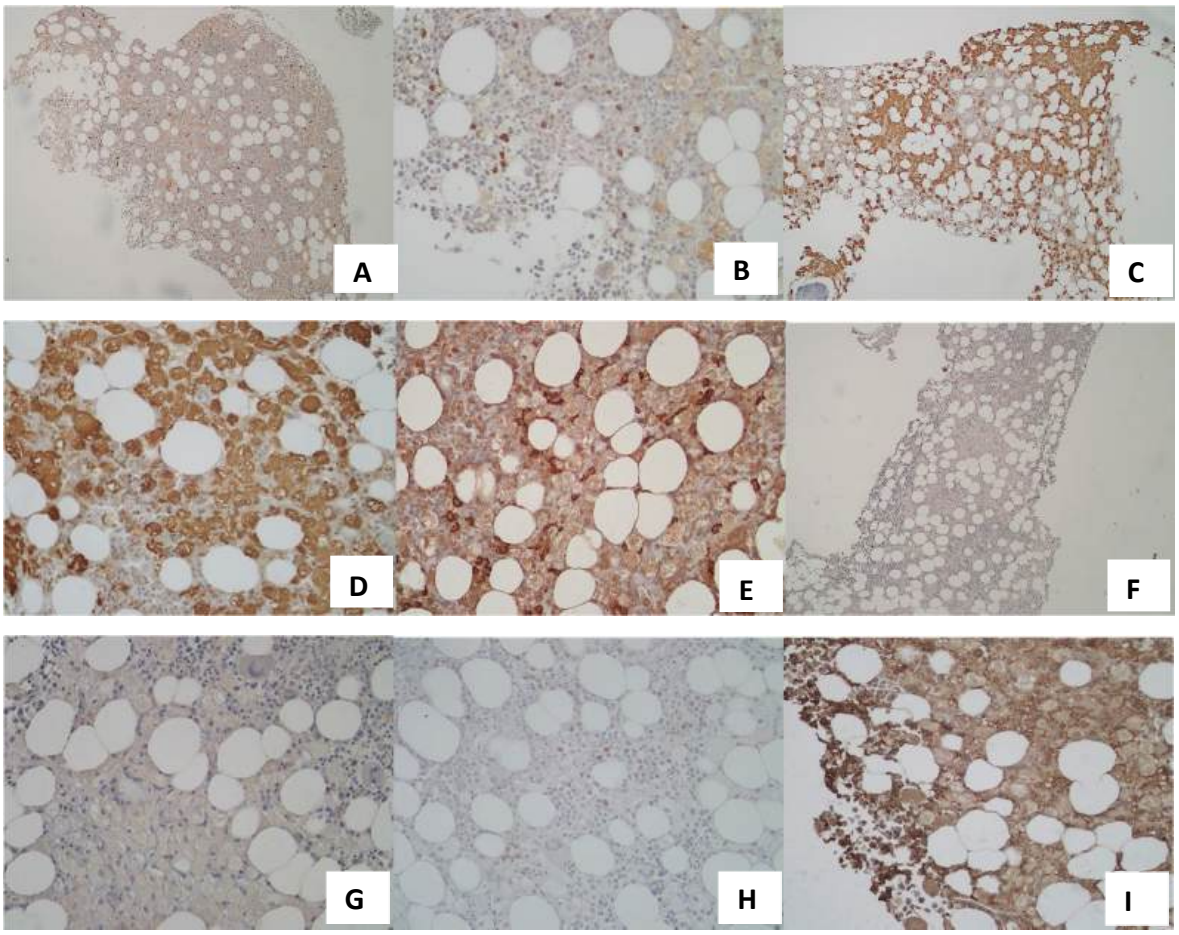

Figure 3. Immunohistochemistry profile. (A, B) Positive CD20 on small scattered lymphocytes, 100x and 400x. (C,D) Positive CD68 in the Gaucher-like cells, 100x and 400x. (E) Positive CD138 on scattered plasma cells, 400x. (F,G) Negative AE1/AE3, 100x and 400x. (H) Positive Ki67 in 5% of cells, 400x (I) Positive Glycophorin A on erythrocytes, 400x.

Other substrates level, globotriaosylceramide (Lyso-Gb3) and lysosphingomyelin (Lyso-SM) levels were slightly increased (1.2 ng/mL; normal <0.8 ng/mL and 15 ng/mL). Diagnosis of Gaucher Disease was established and the patient was submitted to an enzyme donation charity program.

DISCUSSION

Making the diagnosis of GD in this patient was challenging. GD in children is usually presented with delayed growth and development, splenomegaly, and hematologic abnormalities including thrombocytopenia and anemia. However, type I GD has variable age of onset. Thus, adults may also suffer from type I GD. The most common initial clinical presentations of type I GD are splenomegaly, pancytopenia, and hemorrhagic diathesis.[5] Other presentations may be acute or chronic osteopenia,[6] neurological involvement such as extrapyramidal signs, and Parkinsonism.[7] Imaging findings for bone involvement can be identified such as osteopenia/osteoporosis, pathological fractures, focal lytic or sclerotic bone lesions, or osteonecrosis. Erlenmeyer flask deformity at the level of the distal femur is a distinct characteristic (however not pathognomonic) finding.[6]

Lung involvement may occur in type I GD, usually presented as lung interstitial disease and pulmonary hypertension. This mostly occurred in female patients who underwent splenectomy.[8] Type I GD patients may also present with immunological alteration. Gaucher disease is characterized by increased gamma globulin titer and more susceptible to develop plasma cell disorders, such as monoclonal gammopathy of uncertain significance (MGUS)

and multiple myeloma.[9] Metabolic alteration may also occur due to chronic inflammation which induces a hypercatabolic state and reduced body mass. Low high-density lipoprotein and high ferritin with iron overload are frequent. Gaucher disease is also associated with an increased risk of cholesterol-derived gallstones.[10]

Histopathologic features in GD show Gaucher cells in the bone marrow. Gaucher cell is a histiocyte with an abundant granular and fibrillar cytoplasm resembling a crumpled tissue paper. Gaucher cells typically have a single eccentrically located nucleus. It should be distinguished from pseudo-Gaucher cells or Gaucher-like cells. Gaucher cells and pseudo-Gaucher cells are very similar under the light microscopy level on routine Hematoxylin-Eosin staining. Electron microscopical features may also help to distinguish pseudo-Gaucher cells from true Gaucher cells. On electron microscopy, Gaucher cells do not contain typical tubular cytoplasmic inclusions.[11]

These Gaucher-like or pseudo-Gaucher cells can be seen in a variety of conditions such as chronic myeloid leukemia, acute lymphoblastic leukemia, multiple myeloma, myelodysplastic syndrome, thalassemia, and disseminated mycobacterial infection.[12] Pseudo-Gaucher cells in a patient with multiple myeloma has a quite different ultrastructural pattern. They contain crystalloid inclusions that correlate with abnormal kappa light chain precipitations due to sequence mutation. On electron microscopy, they show cytoplasmic crystalline inclusions instead of tubular cytoplasmic inclusion present in Gaucher cells. On routine staining, there are many plasma cells scattered. Patients with mycobacterial infection could also exhibit pseudo-Gaucher cells in bone marrow aspirates. They showed histiocytes with cytoplasms containing needle-like inclusion on electron microscopy.[11,13] These pseudo-Gaucher cells were smaller than typical Gaucher cells. They also showed granuloma on routine Hematoxylin-osin staining.

In a patient with mycobacterial infection, pseudo-Gaucher cells are formed due to inadequate digestion of mycobacterial bacilli by histiocytes and are usually found in a patient with immunodeficiency.[14] In a patient with chronic myeloid leukemia, acute lymphoblastic leukemia, Hodgkin lymphoma, and thalassemia, pseudo-Gaucher cells can also be found in the bone marrow biopsy. Electron microscopy examination of these cells showed elongated lysosomes filled with fibrillary inclusion. Occasional dense rounded structures may also be present. Typical tubular inclusion that presents in the true Gaucher cells cannot be found. These arise under high cell turnover conditions, reflecting an increased load of leucocyte membrane-derived glucosylceramide presented to macrophages.[15-17]

The confirmation of GD requires analysis of β-glucosidase activity or accumulation of glucosylceramide in tissues. In this case, we examined the accumulation of glucosylceramide substrate and the result showed markedly increased glucosyl sphingosine (also-GL1) and slightly increased globotriaosylceramide (lyso-Gb3) and lysosphingomyelin (lyso-SM) levels. Also-GL1 as a relevant biomarker, had been approved with sensitivity and specificity also-GL1 to distinguish GD patients and healthy controls were 100% with cut-off 4 nmol/l.[18] The mechanism of also-GL1 level increasing in GD has also been investigated. Dekker et al and Yamaguchi et al proposed that the major pathway formation of glycol-GL1 was the de-acylation of accumulating glucosylceramide that involves acid ceramidase enzyme.

Lyso-Gb3 and lyso-SM in this patient were slightly increased (1.2 ng/ml and 15 ng/ml).

Lyso-Gb3 was initially used to determine Fabry disease diagnosis. However, the cut-off of less-Gb3 for diagnosis of Fabry disease is >1.3 ng/ml,[19] Also-SM was also used to determine the diagnoses of Niemann-pick disease with a value of 3.3 fold to 100 fold increment in the disease (cut off 16.8 nM).[19,20] Similarly, Polo G et al also stated that Lyso-Gb3 and also-SM levels in plasma GD patients could be normal or slightly increased.[21]

In adults, splenomegaly can be caused by portal hypertension, one of the cirrhosis complications. On the other side, splenomegaly also can be caused by nonportal hypertension,

which one of the causes is Gaucher disease. Bone marrow biopsy to show the Gaucher-like cell and enzyme activity test for confirmation. The therapy of the Gaucher disease is enzyme replacement therapy. One of the enzyme replacement therapy is imiglucerase with an initial dose of 30-60 U/kg intravenous every 2 weeks.[22-24]

CONCLUSION

The finding of CD68-positive in Gaucher-like cells by using the immunohistochemistry staining supporting Gaucher disease. To confirm the diagnosis, an examination of glucocerebroside substrate from the patient's blood plasma was performed. Glucosylsphingosine, a deacylated form of glucosylceramide, was markedly elevated. Therefore, the diagnosis of Gaucher disease in this adult patient in Indonesia was confirmed.

DATA AVAILABILITY

All data generated or analyzed during this study are included within this article.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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A Life-Threatening Complication During the Fourth Pregnancy Due to Acute Promyelocytic Leukemia: A Case Report

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ABSTRACT

Incidents of leukemia in pregnancy are infrequent with only one case found from 75,000 to 100,000 pregnancies. The pathophysiological mechanism of leukemia during pregnancy is still unclear. Leukemia which occurs in pregnancy is usually acute and predominantly the myeloid type.

A 35-year-old woman in her fourth pregnancy with a gestational age of 38-39 weeks, came to the emergency department (ED) with complaints of contractions since 4.5 hours before admission. The contraction was not accompanied by discharge, mucus, or blood, and fetal movements was still active. She denied complaints of fever, nausea, vomiting, dizziness, shortness of breath, weakness, fatigue, lethargy, and bleeding. Physical examination results, both palpebral conjunctiva were pale. Laboratory examination results of a complete blood count, white blood cell count were 2,930/uL, hemoglobin 8.3 g/dL, Hct 24.10%, erythrocytes 2.78x10^6/µL, platelets 62,000/µL. Bone Marrow Aspiration (BMA) revealed Acute Promyelocytic Leukemia (APL).

APL is a subtype of Acute Myelogenous Leukemia (AML). Persistent fatigue, recurrent infections, and bleeding are common manifestations of APL. The diagnosis of APL is made by bone marrow aspiration examination, and it is safe for pregnancy. APL therapy in pregnancy uses All-Trans Retinoic Acid (ATRA) and Arsenic Trioxide (ATO). ATRA and ATO are highly teratogenic, but recent studies have reported no fetal abnormalities.

Accuracy and speed in diagnosing and initiating APL therapy in pregnancy are essential in preventing serious complications.

Keywords *Acute promyelocytic leukemia, pregnancy.*

INTRODUCTION

Incidents of cancer in pregnancy are about 0.07% to 0.1%.[1] Cancer during pregnancy is relatively rare but may lead to maternal mortality.[2] Acute leukemia is a malignancy in the third rank after breast cancer and cervical cancer associated with pregnancy.[3] Leukemia in pregnancy is rare and only found in one in 75,000 to 100,000 pregnancies.[1,3] Leukemia which occurs in pregnant women is usually acute and dominated by the myeloid type. During pregnancy, the incidence of acute leukemia in

the first trimester is 23%, in the second trimester is 37%, and in the third trimester is 40%.[1] Acute promyelocytic leukemia (APL) is a subtype of acute myelocytic leukemia (AML) which is a fatal hematological malignancy. APL is a potential threat to both the mother and the fetus and can cause abortion, premature delivery, intrauterine growth retardation, and death of the fetus and mother if not managed properly. Therefore, APL in pregnancy requires prompt and appropriate diagnosis and therapy.[4,5] However, the diagnosis of leukemia in pregnancy is still quite difficult because the symptoms caused are non-specific and resemble the symptoms that commonly occur during pregnancy. The symptoms that can arise are in the form of weakness, fatigue, shortness of breath, pallor, anemia, thrombocytopenia, and leukocytosis.[1] In addition, APL therapy in pregnancy is challenging and requires attention. The main therapy of APL is chemotherapy, but chemotherapy can also cause teratogenic effects if given during pregnancy.[6]

CASE ILLUSTRATION

A 35-year-old woman in her fourth pregnancy complained of contractions for 4.5 hours before coming into the RSPAL emergency department (ED) on November 27, 2021, at 4:30 a.m. The complaints are felt without being accompanied by her water breaking, mucus, and blood. The patient still felt active fetal movement. The patient denied any complaints of fever, nausea, vomiting, headache, and shortness of breath. A history of bleeding and recurrent infections was also denied. There was no history of hypertension, diabetes mellitus, asthma, or heart disease in the patient, but the patient's mother had a history of hypertension. The patient is taking pregnancy vitamins and iron tablet supplements regularly during this pregnancy. There is no history of drug or food allergies. The patient was married once for thirteen years. The patient had menarche at the age of 13 years with irregular cycles, and the duration of one menstrual period was about 5 days without dysmenorrhea. The first day of the patient's last menstrual period (LMP) is March 6, 2021, and the estimated due date of birth is December 13, 2021. The patients routinely receive antenatal care every month in Surabaya Islamic Hospital. In the first pregnancy, the baby was born full term by cesarean section with an indication of high myopia helped by a doctor in Surabaya Medical Service Hospital. The baby was born male had a birth weight of 3,500 grams and is now 12 years old. In the second pregnancy, the baby was born full term by cesarean section with an indication of high myopia helped by a doctor in Surabaya Medical Service Hospital. The baby was born female with a birth weight of 3,500 grams and is now 9 years old. In the third pregnancy, the baby was born full term by cesarean section with an indication of high myopia helped by a doctor in Surabaya Medical Service Hospital. The baby was born female with a birth weight of 3,500 grams, and now she is 5 years old. Now the patient is pregnant for the fourth time. The patient used a Depoprovera contraceptive injection and then switched to a contraceptive pill but was not consumed regularly.

Physical examination results showed both conjunctiva palpebrae were pale, there was no icterus, cyanosis, or dyspnea. The lymph nodes are within normal limits. Thorax, abdomen, and extremities examination are within normal limits. Then the patient was given a complete blood test on November 27, 2021, the result showed a white blood cell count of 2,930/µL, hemoglobin 8.3 g/dl, Hct 24.10%, erythrocyte $2.78x10^6$/µL, thrombocyte 62,000/µL.

A complete blood count and a peripheral blood smear were carried out on November 29, 2021, at 07:45 p.m., the result showed a white blood cell count of 21,120/µL, hemoglobin 7.4 g/dl, Hct 21.10%, erythrocyte $2.63x10^6$/µL, thrombocyte 20,000/µL. The results of the patient's peripheral blood smear concluded that "suspicious of an APL (*Acute Promyelocytic Leukemia*)" with the suggestion to do Bone Marrow Aspiration (BMA), and *Immunophenotyping*.

The patient received two bags of Packed Red Cell (PRC) transfusion before the active phase of labor on November 29, 2021, and then got an emergency C-section. The baby was born alive with a birth weight of 3,200 grams. After the C-section was performed, the patient was treated in the intensive care unit for recovery caused by heavy bleeding during surgery (1,000 cc). Once stable, the patient is transferred to the puerperal room.

Table 1. The results of hematology analysis (November 29, 2021) with scattergram.

Para.			Result	Unit	Ref. Ranges	
1	WBC	H	50.48	10^3/µL	4.00 - 10.00	Flag
2	Neu#	RH	9.85	10^3/µL	2.00 – 7.00	
3	Lym#	eH	6.46	10^3/µL	0.80 – 4.00	WBC Scattergram Abn
4	Mon#	eH	34.07	10^3/µL	0.12 – 1.20	Blasts?
5	Eos#	RL	0.01	10^3/µL	0.02 – 0.50	Abn Lymph/blast?
6	Bas#	RH	0.12	10^3/µL	0.00 – 0.10	Immature Gran?
7	Neu%	RL	19.5	%	50.0 – 70.0	Atypical Lymph?
8	Lym%	EL	12.8	%	20.0 – 40.0	Leucocytosis
9	Mon%	EH	67.5	%	3.0 – 12.0	Anemia
10	Eos%	RL	0.0	%	0.5 – 5.0	PLT Histogram Abn
11	Bas%	R	0.2	%	0.0 – 1.0	Thrombocytopenia
12	IMG#	R	0.18	10^3/µL	0.00 – 999.99	
13	IMG%	R	0.4	%	0.0 – 100.0	Note:
14	RBC	L	2.56	10^6/µL	3.50 – 5.00	Lym# 13,66; Mon# 5,71;
15	HGB	L	7.1	g/dl	11.0 – 15.0	Lym% 64,7; Mon% 27,0
16	HCT	L	20.2	%	37.0 – 47.0	
17	MCV	L	78.9	fL	80.0 – 100.0	
18	MCH		27.7	Pg	27.0 – 34.0	
19	MCHC		35.1	g/dl	32.0 – 36.0	
20	RDW-CV	H	20.3	%	11.0 – 16.0	
21	RDW-SD	H	57.8	fL	35.0 – 56.0	
22	PLT	RL	32	10^3/µL	100 – 300	
23	MPV	R	8.7	fL	6.5 – 12.0	
24	PDW	R	15.7		15.0 – 17.0	
25	PCT	RL	0.028	%	0.108 – 0.282	
26	P-LCC	RL	9	10^3/µL	30 – 90	
27	P-LCR	R	29.5	%	11.0 – 45.0	
*28	HFC#		****	10^3/µL		
*29	HFC%		****	%		

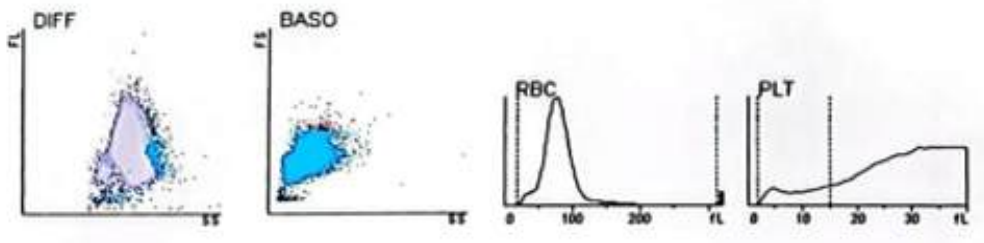

Table 2. Serial complete blood count.

	11/27/2021 at 05:11 a.m	11/29/2021 at 05:10 a.m	12/01/2021 at 07:45 p.m	12/04/2021 at 06:25 p.m	12/05/2021 at 05:20 p.m	12/07/2021 at 06:00 a.m	Unit
White Blood Cell	2,900	9,410	21,120	86,570	118,950	148,760	/µL
Hb	8.30	8.1	7.4	8.0	6.8	9.4	g/dL
Hct	24.10	23.70	21.10	23.50	20.10	27.30	%
Erythrocyte	2.78	2.78	2.63	2.96	2.53	3.33	10^6/µL
Thrombocyte	62,000	46,000	20,000	29,000	36,000	37,000	/µL

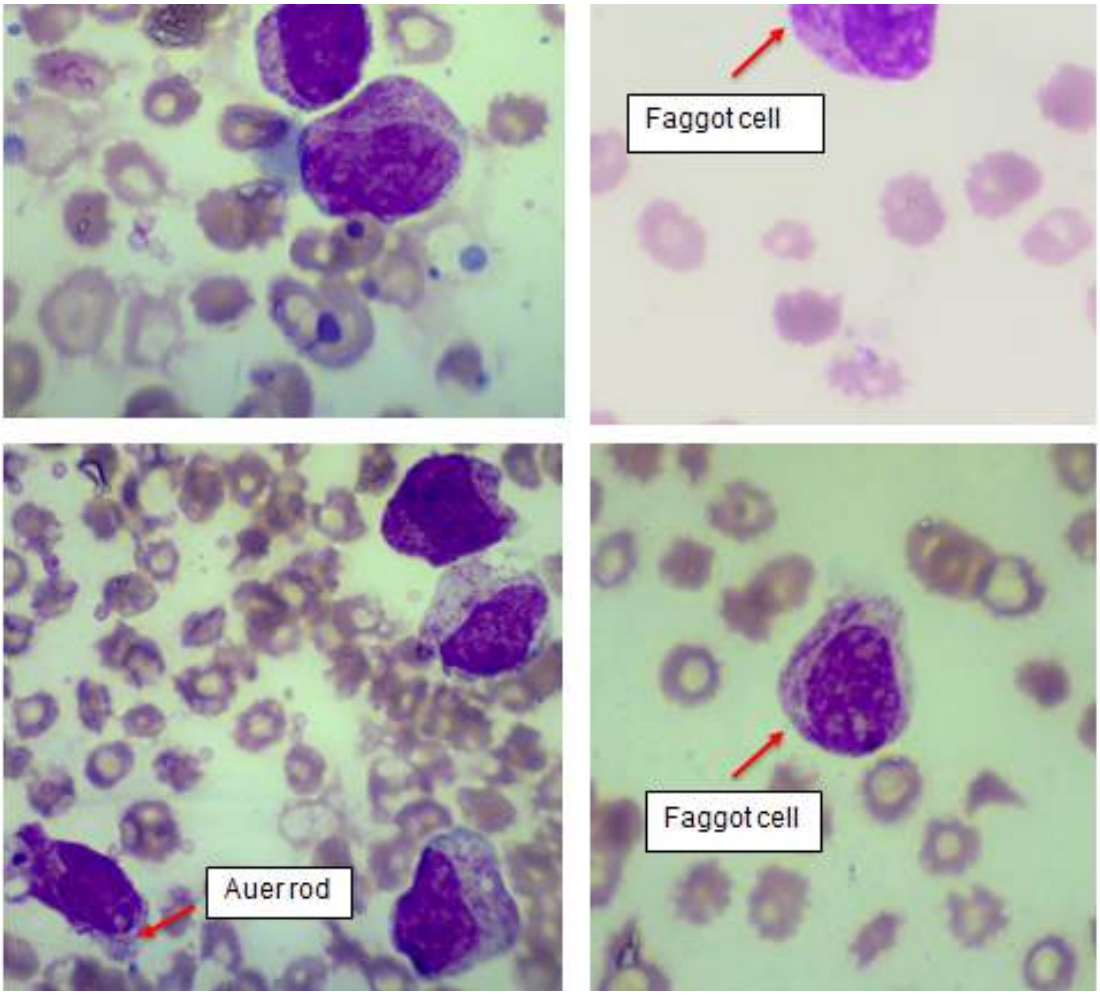

Figure 1 The peripheral blood smear shows promyelocytes, Auer rods (+), and phaggot cells (+).

Then the patient is suggested for bone marrow aspiration (BMA). The BMA was performed on December 2, 2021, with hypercellular results; erythropoiesis system activity was decreased by 2% proportion. Granulopoiesis system activity was increased, the proportion of myeloid series 96%, dominated by hyper granular promyelocytic with proportion 87%, Auer rod (+), faggot cell (+); megakaryopoiesis system activity was decreased. Bone marrow image supported the diagnosis of acute promyelocytic leukemia (APL).

The patient planned to receive chemotherapy but the patient is only able to perform minimal self-care and is confined to a bed or chair for >50% in 24 hours (ECOG 3), so the administration of chemotherapy was postponed. On December 5, 2021, the patient complained of fatigue, fever, and chills. After observing the vital signs at 05:00 p.m., the blood pressure was 98/51 mmHg, pulse 120 beats per minute, temperature 39 ^{0}C, and oxygen saturation was 87%. Then the patient got nasal oxygen 4 liters per minute and oral therapy with folic acid, paracetamol, omeprazole, and myotonic while monitoring the vital signs. At 06:10 p.m., the blood pressure was 100/70 mmHg, pulse 114 beats per minute, temperature 38.2^{o} C, and pulse oximetry showed 92% with oxygen supplementation 4 liters per minute using nasal cannula. On the following day, the patient was transferred to the intensive care unit. The patient died two days later due to sepsis.

DISCUSSION

Leukemia occurred due to the uncontrolled proliferation of white blood cells.[7] Clinically and pathologically, leukemia is classified into four major groups, namely acute myelogenous

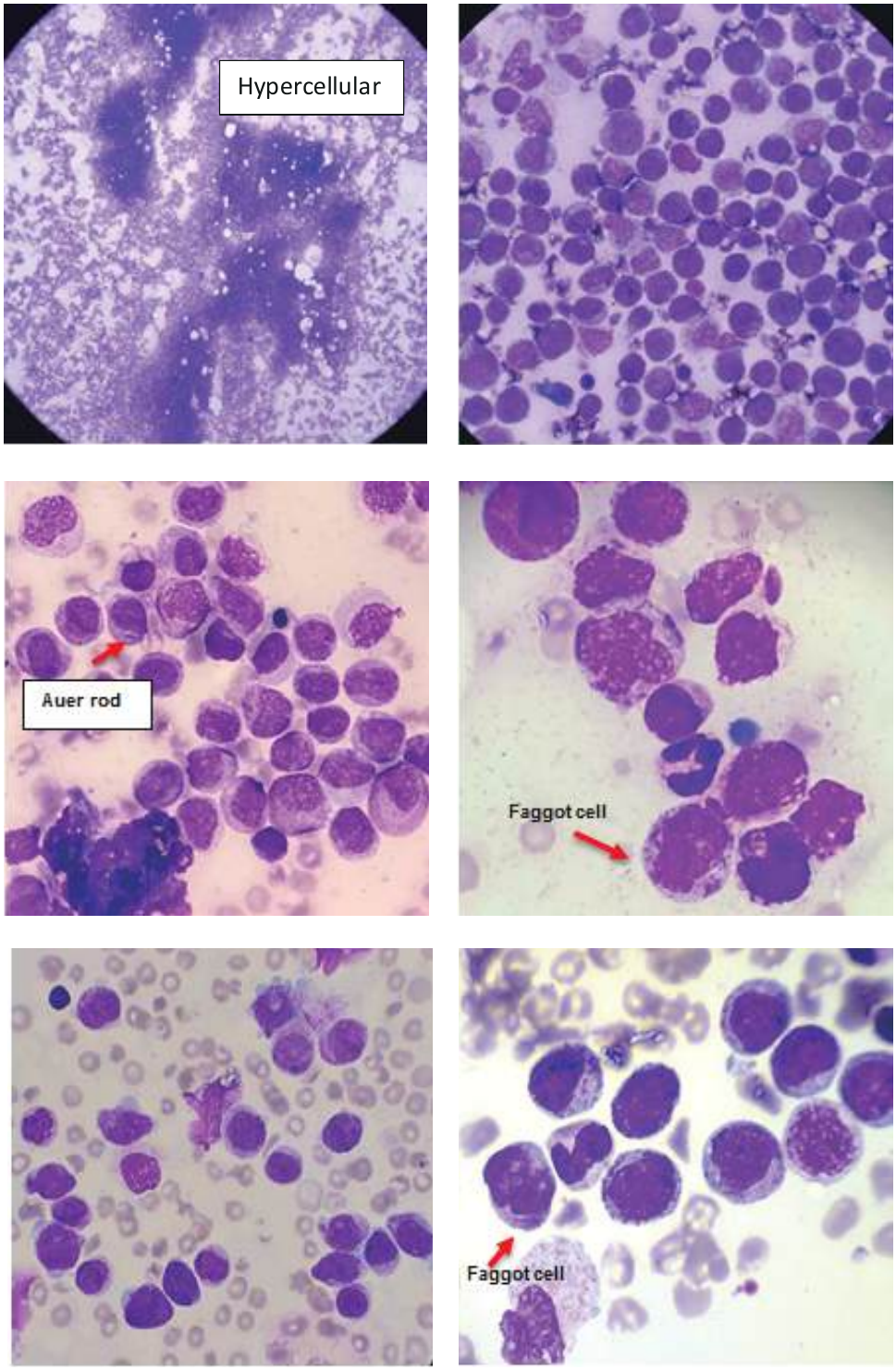

Figure 2. The result of BMA.

leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). ALL and AML are the most harmful types.[8] According to French-American-British (FAB), AML is divided into 8 subtypes, namely minimally differentiated AML (M0), minimally maturing AML (M1), maturing AML (M2), APL (M3), acute myelomonocytic leukemia (M4), acute monocytic leukemia (M5), acute erythroid leukemia (M6), and acute megakaryoblastic leukemia (M7).[9] APL (M3) itself is a unique subtype of AML.[5] APL occurs

due to a translocation between chromosomes 15 and 17 [t(15;17)], resulting in the fusion of the PML-RARA gene. This translocation will stop the development of promyelocytes (immature white blood cells) so that there will be an accumulation of immature white blood cells in the bone marrow.[6]

According to The American Cancer Society, in 2018 there were 19,520 new cases and 10,670 deaths due to AML in the USA and 5-15% of the total cases were APL type. APL is a medical emergency because 17.3% of cases experienced premature death within one month of diagnosis, primarily due to intracranial or severe pulmonary hemorrhage.[10] Cases of acute leukemia in pregnancy are rare, i.e., 1 in 100,000 pregnancies. APL is curable but requires prompt and appropriate diagnosis and therapy.[11] Prognosis in the fetus is strongly related to gestational age; the incidence rate of abortion in the first, second, and third trimesters is 87%, 33%, and 7%, respectively.[6]

The clinical manifestations of APL may include recurrent infections, persistent fatigue, and signs of bleeding. In addition, coagulopathy and petechiae are the most common clinical manifestations of APL. To prevent complications, a fast and precise diagnosis is needed. The diagnostic procedure for APL in pregnancy is no different from that in non-pregnant patients, namely bone marrow aspiration and trephine biopsy can be performed; these procedures are safe during pregnancy. The diagnosis of APL is confirmed when >30% promyelocytic cells are found in the bone marrow peripheral blood smear.[4] In the above case, the patient did not experience obvious manifestations, which the manifestations of her pregnancy may also mask, so the patient came to the hospital not because of complaints about her APL but about her pregnancy. Then it was suspected that she had leukemia when a complete blood test showed abnormalities. Complete blood count errors were denied by re-examination which showed the same result.

APL can occur in all trimesters or during postpartum.[12] APL in pregnancy can create complications for both the mother and the fetus. Infant complications include a higher risk of abortion, perinatal mortality, intrauterine growth restriction (IUGR), preterm delivery, and infection. While the mother bears the risk of perinatal, intranatal, or postnatal mortality. In this case, the patient's condition worsened postnatally and required intensive care. Prior studies consist of a comparison between two cases of APL in pregnancy, those who were immediately treated and those who refused therapy due to the worsening of the condition after being given the first therapy. Patients who resist therapy have a poor prognosis, but patients who receive initial therapy with close monitoring of the mother and baby have a better prognosis.[4] Meanwhile, in our case the patient was diagnosed with APL during his fourth pregnancy and was not recognized early, despite having regular antenatal care. APL symptoms appear during term and in-partum pregnancy and are diagnosed immediately after birth, unlike in prior studies, the patient was detected and diagnosed at 34 weeks gestation. In another prior study, the patient came with secondary postpartum bleeding for 6 days and there was bleeding in the gums and hematemesis. The patient was planned for chemotherapy with ATRA but the patient's condition worsened and finally died.[13] This case was almost the same as our case, the patient was just diagnosed postpartum and was planned for chemotherapy but the patient got worse and eventually died. The explanation for why APL appeared at the fourth postpartum is not known in our case.

Treatment of leukemia during pregnancy requires multidisciplinary collaboration. Chemotherapy is the primary treatment for leukemia. Chemotherapy uses cytotoxic chemicals which have numerous adverse effects on both the mother and the fetus, particularly in the first trimester (2-8 weeks). Physiological changes in the mother during pregnancy such as increased plasma volume, the presence of amniotic fluid, hepatic oxidation, and changes in renal clearance, might impact drug metabolism, distribution, and excretion.[14] Treatment of APL in adults is divided into induction and post-remission (consolidation and maintenance) therapy. Induction therapy was administered for four weeks using a combined regimen of ATRA (All-Trans Retinoic Acid) and ATO (Arsenic

Trioxide). As an alternative, anthracycline, cytarabine, and hydroxyurea can be used. Consolidation therapy using a combination of ATRA and ATO for 7 months, and maintenance therapy using a combination of ATRA with 6-mercaptopurine and methotrexate for 2 years.[5]

ATRA is highly teratogenic causing fetal retinal damage, neural tube defects, cardiovascular malformations, craniofacial deformities, renal diseases, psychological disorders, and thymus gland aplasia. This can happen if ATRA is utilized during the first trimester. Therefore, avoid using ATRA in the first trimester and start it in the second and third trimesters, while keeping tight control of the baby's heart rate.[15] However, no congenital problems were found in several previous studies on the use of ATRA in APL pregnancies. Pregnant women get the same dose of ATRA as other patients, specifically 40-45 mg/m^2/day. ATO, like ATRA, is extremely teratogenic and should be avoided during all trimesters of pregnancy. However, prior studies reported the birth of babies without any abnormalities from APL mothers who were treated with a combination of ATRA and ATO. The ATO dosage reported that does not induce fetal abnormalities is 8 mg/day.[5]

Chemotherapy for APL in pregnancy can be started when the gestational age is above 10 weeks because the 10th week of gestation is the time of the most active growth and development of the fetus. If APL is identified in the second or third trimester, chemotherapy can begin immediately.[5] However, if APL is identified during postpartum, chemotherapy can begin immediately, however, it is ensured that the patient is not breastfeeding her child.[15] However, if the mother's condition is critical, chemotherapy can begin in combination with other supportive symptomatic care, and the pregnancy can be terminated after her condition has stabilized.[5] In determining the patient's condition, ECOG (Eastern Cooperative Oncology Group) Performance Status can be used, which consists of grade 0 (very active, the patient can do all activities without limits) to grade 5 (the patient died). Chemotherapy can only be given to patients with ECOG grades 0-2.[16] In our case, the patient was diagnosed with APL during postpartum, and the patient's condition worsened with the patient's ECOG performance status of 3, so chemotherapy administration had to be postponed.

CONCLUSION

Dealing with APL cases during pregnancy is challenging since getting a diagnosis requires speed and precision. On the other hand, the clinical manifestations may be nonspecific. Furthermore, in this type of APL, precision and quickness in initiating therapy are required to prevent complications.

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Endoscopic Dilatation with Ultrathin Endoscope Assisted Method for Esophageal and Pyloric Stricture related Corrosive Injury: 4 Years Case Series Study

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ABSTRACT

Corrosive injuries (CI) become medical problems related complications include esophageal, pyloric stricture and squamous cell carcinoma, physical and quality of life. Endoscopic (ED) dilatation is primary therapy. The ultrathin endoscope-assisted method is potentially safe and useful in avoiding technical failure. Describe clinical outcomes of ED ED-related CI including successful, refractory, recurrent, and complications-related procedures. Case series study of esophageal and/or pyloric stricture patients after CI who underwent dilatation at Soetomo General Hospital (July 2018 – July 2022). One – biweekly ED using Through The Scope (TTS) balloon or Savary Bougie dilator. The target diameter is 14mm. Fifteen patients with stricture-related CI. Eleven patients underwent ED with a total of 73 procedures. Mean age 31,45 years, predominantly male patients (6), suicide attempt (7), acid agent (9), located at esophagus (3), pylorus (3), or both (5). Number of esophageal dilatation to achieve the target of 14 mm was 1-2 and 2-15 procedures for simple and complex stricture. Five esophageal strictures were successfully dilated but 2 patients were recurrent and 3 cases were refractory to ED. Pyloric dilatation resulted in a lower success rate. Recurrent and refractory cases were 5 and 3 patients respectively. ED with ultrathin endoscope method is useful for traversing guidewire during ED. Ongoing inflammation and fibrosis were linked to recurrent and refractory stricture.

***Keywords**: Corrosive injury, dilatation, esophageal, pyloric stricture.*

INTRODUCTION

Corrosive injuries still become medical problems in the acute phase and also delayed complications include esophageal, pyloric stricture, and squamous cell carcinoma,[1] impairing social, physical, emotional, and quality of life.[2] About 13.5% - 22% of the patients will develop strictures.[4-6] Strictures on the esophagus and pylorus are the most prevalent delayed sequelae and endoscopic dilatation is the primary therapy.[7]

In the last 4 years (2018-2022) there were

36 corrosive injuries at the Endoscopy unit of Dr. Soetomo General Hospital Surabaya with 15 (41.6%) strictures on the esophagus, pylorus, or both. Esophageal strictures related to corrosive injury are frequently long, tight,[8,9] and multiple sites, which require endoscopic or surgery intervention.[2,10] Endoscopic dilatation is the first-line therapy for stricture-related corrosive injury.[2] However, due to tight, long, or tortuous stricture and insufficient visualization of the distal side of the lesion, endoscopic management is not always possible[4] and treated under fluoroscopy to ensure proper guidewire placement before dilatation. Because radiologic facilities are not available in most endoscopy units, the initial assessment and treatment may be delayed.[11] One of the most important steps in dilatation is the proper placement of the guide wire beyond the stricture.[4] The ultrathin endoscope (≤ 6mm) could pass through the stricture easier than a conventional endoscope, allowing the guide wire to be inserted, evaluate the distal side of the lesion, and measure the length and characteristics of the stenosis.[4]

This study will describe the clinical outcome of endoscopic dilatation with Ultrathin Endoscope Assisted Method including clinical improvement, success rate, refractory rate, recurrent rate, and complications during and after procedures.

METHODS

Case series study of patients with esophageal and/or pyloric stricture after corrosive injury who underwent endoscopic dilatation at Soetomo General Hospital from July 2018 – July 2022.

Data such as age, gender, caustic agent, type of stricture, number of dilatations, increasing of body weight and outcome of endoscopic therapy were recorded.

Anatomical type of stricture was classified into simple and complex. Simple strictures are the symmetric or concentric, short, diameter of 12 mm or more and easily passed by an endoscope. Complex structures are asymmetry, diameter <12 mm, or inability to pass an endoscope.[12]

All procedures were performed under general anesthesia. First, conventional gastroscope (GIF-HQ190, Olympus) was inserted into the stricture area. If conventional endoscope guide wire insertion failed, and an ultrathin endoscope (GIF XP260; Olympus) was traversed and approached directly in front of the stenotic lesion orifice. The guidewire was inserted through the working channel of the ultrathin endoscope and then removed completely, leaving the guide wire in place.

The opposite side of the guide wire was grabbed and retrieved through the working channel of the conventional scope.[4]

Endoscopic dilatation was performed using Through The Scope (TTS) balloon dilator or Endoscopic bougie dilatation. An endoscopic TTS balloon dilator was inserted using a guidewire through an accessory channel with a minimum of 5 mm to a maximum of 18 mm diameter. The dilator was slowly inflated with liquid to certain pressures, usually 1, 2, and 3 atmospheres, and maintained for 2–3 min and then deflated. The procedure will be repeated two or three times with a stepwise larger pressure to achieve the target diameter gradually from gradual stepwise dilatation from a 75 diameter of 5 mm to 7, 9, 11-, 12.8-, 14, and 15-mm.[13]

Endoscopic bougie dilatation was performed with a Wire-guided Polyvinyl dilator Savary-Gilliard/SG. The scope was introduced to evaluate the anatomy, and then the bougie dilator was passed over the metal guidewire. The first dilator was chosen based on the estimated diameter of the esophageal stricture. The sensation of resistance during dilatation on this dilator protects from over-dilatation.[10] To prevent adverse events particularly perforation we use the "Rule of Three" which means that the stricture is dilated no more than 3 mm per session using three consecutive bougies once moderate resistance is encountered.[14] After dilation, the endoscope was inserted to evaluate the dilatation and complications such as bleeding or perforation. Bougie dilation was the first choice to stretch the simple esophageal stricture. The tortuous, long esophageal stricture or pyloric stricture was dilated with a balloon dilator. One week after the first dilation, patients were advised to return to the hospital for endoscopic evaluation and re-dilatation until the target diameter of 14mm was

achieved. Triamcinolone acetonide was injected into the surrounding stricture area (4 quadrants, 20mg each).[8] All patients had written informed consent before endoscopic dilatation.

We followed the Kochman criteria definitions for refractory and recurrent strictures. The refractory stricture was classified if the diameter of the stricture could not reach 14 mm over four sessions of dilatation. Recurrent stricture happens if it cannot maintain a luminal diameter for 4 weeks once the target diameter of 14 mm had been achieved.[15] Esophageal dilatation can be performed under the combination endoscopy and fluoroscopy or endoscopy alone.[10]

Successful Outcome was defined as relief in dysphagia, increasing body weight, or achieving a diameter of 15 mm after endoscopic dilatation without requiring endoscopic procedure or surgical intervention for at least 6 months.[2]

RESULTS

There were 15 patients with stricture-related corrosive injury with a total of 73 dilatation procedures. Three patients were referred to digestive surgery because of near-total obstruction with diffuse mucosal injury, whereas 1 patient refusedendoscopic dilatation. Eleven patients underwent endoscopic dilatations. Most dilatations were performed 6 months after injury (range 1 month to 1.5 years). Three patients had psychiatric problems (Schizophrenia paranoid, Baby blues syndrome, and Bipolar disorder) **(Table 1)**.

Two patients with simple esophageal stricture successfully dilated with SG dilator and scope dilatation in 1 session. Six patients had complex esophageal strictures with 5 of them located at two or more sites along the esophagus**. (Table 2)**

In complex stricture with very tight diameter we use slim scope, guidewire, and fluoroscopic guidance then introduce a TTS balloon dilator until a certain diameter which SG dilator can pass the stricture. As the diameter became larger then SG dilatation was inserted to achieve target diameter **(Figure 1)**.

Table 1. Clinical characteristics of patients with strictures related to corrosive injury.

Characteristics	Results
Age	Mean 31.45 years
Sex	
Male	6
Female	5
Mode	
- Suicide attempt	7
- Psychiatric disorder	3
- Accidental	1
Time after injury to dilatation	
- 1-6 months	6
- 7-12 months	1
- > 12 months	2
- Not known	1
Location	
- Esophagus	3
- Pylorus	3
- Esophagus & pylorus	5
Agent	
- Acid (HCl 8.3% - 20 %)	9
- Alkali	1
- Unknown	1
Symptoms	
- Dysphagia	11
- Decreasing of body weight	11
Body weight	
- Before dilatation	Mean 46.6 kg
- fter Dilatation	Mean 51.9 kg

The Number of dilatations to achieve the target of 14 mm was 1-2 and 2-15 for simple and complex esophageal stricture respectively. The number of dilatations was higher if the diameter of esophageal stricture was less than 0,6mm or long stricture. The time from injury to dilatations was an important factor because corrosive injury resulting an inflammatory and fibrotic process that continues several months after injury. Overall successful, recurrent, and refractory cases for esophageal dilatations were 7, 2, and 3 patients respectively **(Table 2)**.

For recurrent and failure to dilatation stricture we consider continuing endoscopic dilatation accompanied by Triamcinolone acetonide injection since the inflammatory and fibrotic process have not yet subsided.

Abdominal CT scan was performed for recurrent and refractory stricture to evaluate the characteristics of the stricture. Retrosternal pain after the procedure was recorded in 1 patient without any sign of perforation.

Pyloric Strictures

Most of the pyloric strictures were complex and tight strictures. **(Figure 2).** Pyloric stricture (alone or combined with esophageal stricture) resulted in a lower success rate than esophageal dilatation. Five patients had recurrent and 3 patients had refractory pyloric stricture respectively. **(Table 2).**

Two patients were referred to digestive surgery because of the progression of the stricture with complete luminal stricture and the inability to identify the luminal orifice to insert a guidewire. These patients delayed their endoscopic schedule by themselves due to the pandemic while the fibrotic process progressed.

One patient was a candidate for surgery although there was an improvement in dysphagia and increasing in body weight. There was increasing in mean body weight after dilatation as an improvement of dysphagia symptoms **(Table 1)**.

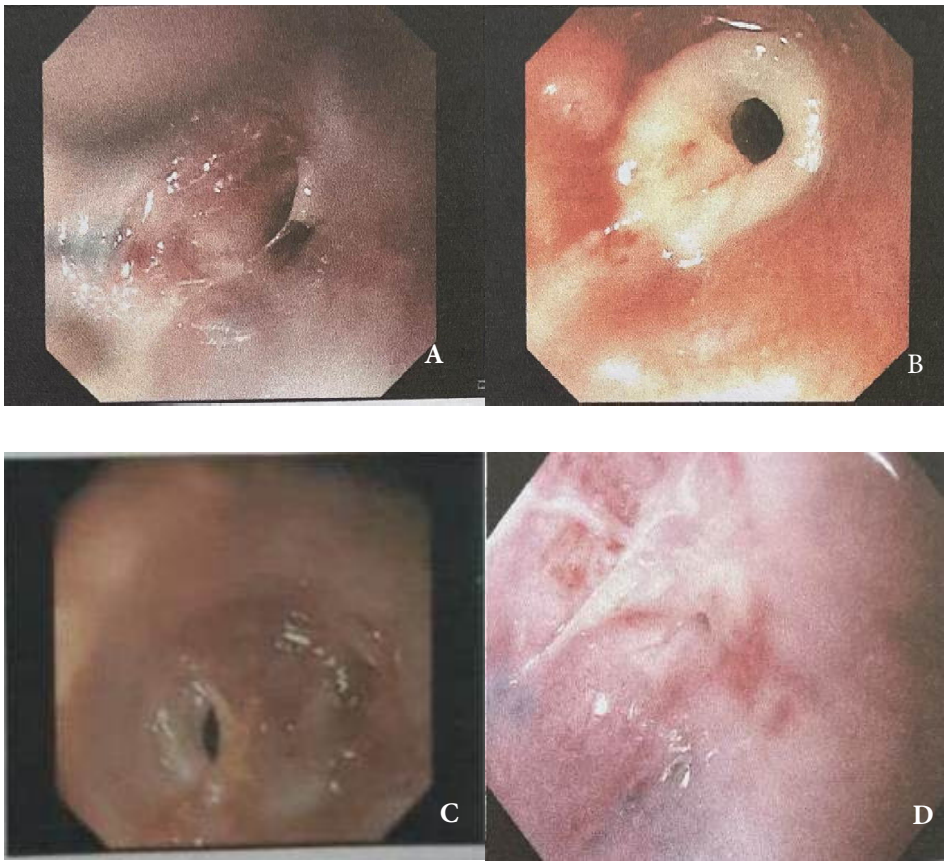

Figure 1. Esophageal stricture with tight diameter, surrounded by fibrotic scar.

Table 2. Esophageal and pyloric stricture and clinical outcome.

Stricture	Frequency (%)	Method	Number of dilatations to achieve target (Range)	Success (%)	Recurrent (%)	Refractory (%)
Esophagus						
Simple	2	SG Scope dilatation	1-2	2 (100)	0	0
Complex	6	SG TTS balloon	2-15	5 (83)	2 (33.3)	3 (50)
Pylorus						
Simple	2	TTS balloon	1-2	2 (100)	0	0
Complex	6	TTS balloon	2-17	3 (50)	5 (83.3)	3 (50)

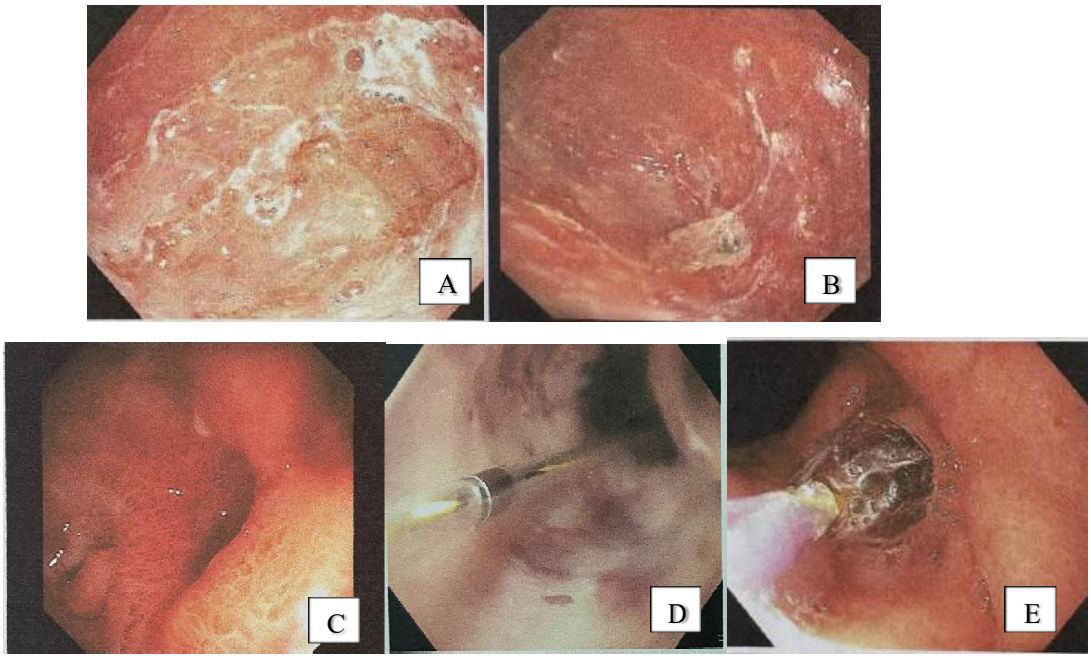

Figure 2. Pyloric stricture with tight diameter (A-C). Pyloric stricture with TTS balloon in place and direct visualization (D, E).

No complications such as infection, mediastinitis, or perforation were observed during or after the dilation sessions.

DISCUSSION

The corrosive injury occurs when a wide range of chemical substances with pH<2 or pH>12 are swallowed accidentally or suicide attempt and cause tissue damage and destruction. Adults between the ages of 30 and 40 typically ingest strong corrosives with suicide attempts and present with severe, life-threatening injuries.[6] Due to the 'liquefaction necrosis' of alkaline substances, corrosive injury from alkali can be more damaging to the gastrointestinal tract than 'coagulation necrosis' from acid ingestion. Previous reports suggest that alkali usually destroys the esophagus, while acid primarily damages the stomach. But in case of massive ingestion, both acids and alkalis may cause extensive necrosis of the gastrointestinal tract. Strong acids result in coagulation necrosis that protects the esophagus from damage and penetration to the deep layer. The epithelial

layer and the alkaline pH on the esophageal wall had a protective effect. However, this study showed that acid substances had a destructive effect on both esophagus and gaster in almost similar proportions. Gastroesophageal reflux of corrosive agent due to impaired lower esophageal sphincter and motility dysfunction resulted in corrosive injury and stricture at the esophagus as well as gastric injury. Pyloric spasm prolonged gastric contact time and this explained the pyloric involvement in 8 patients in this study.[6,16] Corrosive injury located at the duodenum appeared to be rare and less severe because of pyloric spasms.[10] In this study, the dominant causative agents are strong acid substances (Hydrogen Chloride 8.3% -20%) from household cleaning that are easily accessible.

Acid ingestion is more common in Asian countries while alkali account for most severe caustic injuries in Western Europe and South America.[6,10] After strong corrosive agent ingestion, the esophagus can be divided into 3 stages as follows: (1) Acute necrosis and thrombosis occur 1-4 days after ingestion; (2) ulceration and granulation phase occur in 3-12 days. During this stage, mucosal shedding, bacterial colonization, and granulation formation are evident. The esophagus is in its most fragile stage. All operations such as laparoscopy or dilatation must be performed very carefully; (3) the healing period begins 3 weeks after the injury. It usually takes 1-6 months for the wound to heal completely. Any surgical attempt for non-dilatable stenosis should wait until after this period.[10]

During the third week, scar retraction leads to stricture formation and progresses over several months. Esophageal dysfunction due to scarring combined with gastroesophageal refluxwill accelerate scarring.[6]

The severity of the injury depends on the acidity of the agent, contact time, amount, and purpose of ingestion. The purpose has an important predictor and intentional ingestion (suicide); which is the mode of ingestion in this study is correlated with severe injury and stricture.[13,6] Patients at risk for stricture had a high endoscopic grade, consumed strong acids or alkalis, had leukocytosis, and had a low thrombin ratio.[10] The severity of esophageal wall stricture is determined by the depth of necrosis. In 100% of cases, full-thickness necrosis causes strictures and even perforation within 2 to 4 weeks.[16] The likelihood of developing a stricture after an esophageal burn of grade 2B and grade 3 may be 71% and 100%, respectively.[17]

Corrosive strictures can involve all oesophageal segments, multiple, long, irregular, and frequent refractory to dilatation compared to other causes of benign stricture. Dysphagia and decreasing body weight are the most common symptoms related to esophageal stricture or gastric outlet obstruction related to pyloric stricture. The most relevant symptom is progressive dysphagia to solid food, and this sometimes progresses to involve semisolid and liquid foods.[14] Some patients may present with nutritional deficiencies and weight loss in addition to persistent dysphagia or odynophagia.[18]

Endoscopic dilation is the first-line management option. Early endoscopic dilatation effectively prevents surgery. The best time for dilatation is after the acute injury has healed, which is usually around the third week. Late management is associated with significant fibrosis and collagen deposition in the esophageal wall, necessitating more endoscopic sessions for adequate dilatation and resulting in a significantly higher number of refractory and recurrent strictures. The practice is supported by the majority of evidence-based guidelines.[2,7,19] Other endoscopic modalities for esophageal strictures currently include needle knife dissection, argon plasma coagulation (APC), temporary stent placement, laser cannulation, and self-dilation. However, treatment options are limited if a complete luminal occlusion occurs.[20]

In this study 6 patients were admitted to the hospital and underwent endoscopic dilatation 1-6 months after injury. The improvement of symptoms and nutritional status is the main goal of treatment rather than conserving large oesophageal lumen patency.[6] A study by Tharavej et al reported that the majority of patients with acid-induced corrosive esophageal stricture required more sessions and were frequently refractor to dilatation. Esophageal dilatations were successful in one-fourth of the patients.

Concomitant cricopharyngeal stricture, long stricture, requiring frequent dilatation, and refractory to >11 mm dilatation were factors associated with failed dilatation.[13]

The type of dilator used will be determined by availability and experience with the particular device. There is no agreement on how these patients should be followed up. We do a dilatation program for short intervals (weekly or biweekly) until the ultimate goal of elimination of dysphagia is achieved then extended three weekly, one month, two months, or three months until persistent improvement and are already asymptomatic.

Esophageal dilatation using Savary bougies is preferred to balloon dilators although studies have shown no clear advantage of one method over the other.[6] Systematic review and meta-analysis showed that there was no difference in symptomatic relief, recurrence rate at 12 months, bleeding, or perforation between bougie and balloon dilation of benign esophageal stricture.[21] Balloon dilators delivered a radial and simultaneous dilating force across the entire length of the stricture, whereas bougie dilators delivered both a radial and a longitudinal force from the most proximal to the most distal portion of the stricture.[5] Joshi et al reported endoscopic dilatation with SG dilators was successful in 71.8% of patients whereas refractory and recurrent strictures were 1.5% and 7.8% respectively. Endoscopic dilatation outcome was associated with increasing stricture length (more than 6 cm).[2]

The ability to traverse any esophageal stricture is determined by the stricture's complexity.

Endoscopically, the presence of a patent lumen within the stricture and the diameter of the lumen are two important factors that determine the methods and success of traversing the stricture. As a result, the preferred techniques for traversing esophageal strictures will differ depending on whether the strictures are simple, complex with patent lumen, or complex with complete occlusion.[9] In this study, there were 6 complex esophageal strictures and 5 patients were successfully dilated.

Recurrent esophageal stricture in 2 patients happened 3 - 4 weeks after the target diameter was achieved. The strictures were complex, long, and multisite. Recurrent pyloric stricture was earlier and more frequent than esophageal stricture due to ongoing inflammation and fibrotic processes. (**Table 2)**. Although endoscopic balloon dilatation is effective in treating gastric outlet obstruction in patients with short strictures perforation and failure are common.[6] We recorded 1 patient with retrosternal pain without any sign of perforation.

Recurrent and refractory stricture after endoscopic dilatation needs further investigation and treatment. The response to dilatation can be predicted using CT or endoscopic ultrasound wall thickness. Patients with an esophageal wall thickness greater than 9 mm on CT scan required significantly more dilatations than those with a wall thickness less than 9 mm.[22] There are no established guidelines for the treatment of refractory strictures.[8] The emergence of interventional endoscopy has renewed interest in intraluminal stenting to prevent stricture recurrence after dilation. Although silicone rubber, polyflex, and biodegradable stents have shown promising results, their widespread clinical use is currently inhibited by issues such as hyperplastic tissue growth, removal difficulties, a high migration rate (25%), a high recurrence rate (50%), low availability, and high costs.[6]

Endoscopic stent placement can improve the duration of time without symptoms, dilate the stricture segment repeatedly, and reduce the suffering caused by repeated dilations. Most medical professionals believe that 4 to 8 weeks is the right amount of time for the esophageal stent to remain in place. If the duration is too short, the cicatricial tissue in the stricture segment cannot be organized completely, which increases the risk of recurrent strictures, and if the duration is too long, serious connective tissue proliferation is inevitable and stent removal becomes challenging.[2] Recurrence rates of refractory strictures after stent removal are as high as 69%, particularly in patients with long strictures (>7cm).[19] Intralesional steroid injections enhance the effects of endoscopic dilation, and topical mitomycin can be effective in the treatment of complex strictures; such combined approaches should be discussed before deciding on surgery.[6] Steroids had an inhibitory

effect on the inflammatory response to reduce stricture formation, collagen synthesis, fibrosis, and chronic scarring.[14]

It has been suggested that dilatations should be stopped and reconstructive surgery should be considered after five to seven unsuccessful sessions. However, additional patient-related considerations like age, malnutrition, and operative risks, as well as the surgeon's experience and the availability of other surgical choices.[6] In this study, 2 patients with recurrent and refractory stricture refused to perform digestive surgery and continued dilatation procedures. In the 15th session, the target dilatation was achieved.

Patients with dilatation failure may undergo esophageal replacement surgery using stomach, jejunum, or colonic conduits. In patients requiring esophageal replacement surgery, the timing of surgery, resection or bypass, type of conduit and route of placement, as well as the site of proximal anastomosis as determined by the extent of caustic injury to the hypopharynx and proximal esophagus, should all be carefully considered. A gastric pull-up is usually preferred in patients with isolated esophageal involvement, low stricture, and a normal stomach, whereas patients with pharyngo-esophageal strictures or combined esophageal and stomach involvement require a colonic conduit.[2] Regarding the adverse event, there was 1 patient with retrosternal chest pain and relieved with a killer drug. No perforation nor mediastinitis was recorded.

CONCLUSION

Endoscopic dilatation with ultrathin-assisted method is useful to traverse guidewire through the stricture. Because stricture-related corrosive injury frequently has complex anatomical structure, more sessions are required, especially if the inflammation and fibrotic process have not subsided. Further studies with more samples are needed to determine factors correlated with clinical outcomes.

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Secondary Polycythemia and Non-Islet Cell Tumor-induced Hypoglycemia in Advanced Hepatocellular Carcinoma: A Case Report

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ABSTRACT

Continuously holding its position as the sixth most common cause of cancer and the third leading cause of cancer death, globally, Hepatocellular Carcinoma (HCC) remains as a healthcare priority. Production of various substances may result into systemic or metabolic complications, often known as paraneoplastic phenomena of HCC.

A 56-year-old male with history of untreated chronic hepatitis B arrived with generalized weakness and intermittent headache in the last two days prior to admission. Laboratory findings demonstrated elevated hemoglobin (20.5 g/dl), alpha-fetoprotein (29,845 ng/dl), and d-Dimer (2,120 ng/ml) levels. Hypoglycemia (44 mg/dl) was documented with normal basal insulin level, confirming non-islet cell tumor hypoglycemia. Abdominal multiphasic CT-scan demonstrated a large solid lesion involving the whole right liver lobe, hyper-enhanced at arterial phase and wash-out pattern at venous and delayed phases, with portal vein thrombosis; thus, confirming HCC BCLC C. Further examinations revealed hypercellularity from bone marrow biopsy with the absence of JAK2 mutation. He underwent serial phlebotomy and received 80 mg acetylsalicylic acid orally, as well as cytoreductive agent to reduce the risk of thrombosis. Despite applications of different interventions, control of hypoglycemia could not be achieved without parenteral administration of high dextrose load. He was planned to receive oral multikinase inhibitor, however, he passed away due to severe hospital-acquired pneumonia.

Paraneoplastic phenomena are common in HCC. Increased risk of blood hyper-viscosity and thrombosis attributed to polycythemia, as well as medical emergency resulting from hypoglycemia showed that both conditions should not be overlooked since they may worsen the patient's prognosis.

Keywords: *Hepatocellular Carcinoma, Secondary Polycythemia, Secondary Erythrocytosis, Non-Islet Cell Tumor-Induced Hypoglycemia.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common liver-related malignancy worldwide, including in the Southeast Asia region. Aside from continuously increasing annual incidence, HCC also maintains its position as the sixth most common malignancy and the third most common cause of cancer-related death globally.[1,2] In the last two decades, the increased global healthcare burden due to HCC has been mainly affected by a higher incidence rate of HCC-related risk factors, for instance, chronic hepatitis B, chronic hepatitis C, or non-alcoholic steatohepatitis. Additionally, many HCC patients only came to seek medical assistance after clinical manifestations had occurred, in which most of them had already been in advanced stages with small opportunities to perform potentially curative therapies.[3] In Indonesia itself, the incidence rate of HCC is estimated to be as high as 10.4 cases per 100,000 person-years.[1]

One of the events that can result in worsening clinical progression of HCC patients is paraneoplastic phenomena. Paraneoplastic complications may occur in the form of systemic and metabolic events as a direct or indirect effect of the release of abnormal substances by tumor cells to extracellular organs through the bloodstream.[4] Aside from being widely known as oncologic emergencies, previous studies demonstrated paraneoplastic phenomena as a clinically and statistically significant independent predictor of worse prognosis in HCC patients with 36 days of average survival. The most common paraneoplastic phenomena in HCC patients are polycythemia or erythrocytosis, hypoglycemia, hypercholesterolemia, and hypercalcemia.[4,5] The case that will be discussed in this report will highlight the importance of early detection of paraneoplastic phenomena in HCC patients, particularly polycythemia and recurrent hypoglycemia, as well as their implications on the care plan of the patients.

CASE ILLUSTRATION

A 56-year-old male arrived with the chief complaint of worsened generalized weakness in the last two days before hospital admission. The patient reported recurrent headaches with a Visual Analogue Scale (VAS) of 3-4 without any sign of central involvement. Significant weight loss (approximately 10 kg) was reported in the last three months, accompanied by an enlarged mass in the right upper quadrant of the abdomen and chronic pain (VAS 4-5). Past medical history of untreated chronic hepatitis B infection in the last four years before hospital admission. He also had a family history of his older brother with liver cancer, as well as smoking habits and alcohol consumption for more than two decades.

Clinical examination demonstrated normal vital signs and a stable hemodynamic state. His functional status score was 2 according to the Eastern Cooperative Oncology Group (ECOG) classification. Abdominal examination revealed an immobile, hard, and irregular hepatomegaly with dilation of collateral veins. Splenomegaly was identified at Schaffner 2. There was also pain upon palpation of the right hypochondriac region. Skin examination demonstrated multiple plethoras on both of his upper extremities without any pain upon palpation. Pitting edema was observed on both of his lower extremities.

Laboratory examinations showed a significant increase in hemoglobin (20.5 g/dl) and hematocrit (65.8%) levels. We found hypoalbuminemia (2.6 mg/dl), increased levels of total bilirubin (2.41 mg/dl) and direct bilirubin (1.44 mg/dl), as well as increased d-Dimer level (2,120 ng/ml). A peripheral blood smear examination indicated polycythemia with thrombocytopenia. Hypoglycemia of 46 mg/dl was noticed, and he was immediately resuscitated with intravenous dextrose infusion. Further examination showed a normal basal insulin level (20 mIU/ml). His serology results showed reactive hepatitis B surface antigen (HBsAg), non-reactive hepatitis B e-antigen (HBeAg), reactive anti-hepatitis B e-antigen (anti-HBe), together with a high quantitative HBV DNA level of $4.72x10^4$ IU/ml. Serum alpha-fetoprotein (AFP) level was significantly increased (29,845 ng/ml).

Multiphasic upper abdominal Computed Tomography (CT) scan demonstrated a large-sized lesion, involving almost the whole portion of the right liver lobe with a hypervascularity appearance on arterial phase and wash-out appearance on venous and delayed phases.

Additionally, there were multiple satellite nodules on the second, seventh, and eighth segments of the liver (**Figure 1**). The radiographic findings also showed a right portal vein tumoral thrombus (**Figure 1(d), 1(e)**). Another tumoral thrombus was also seen on the inferior vena cava, located as high as the inter-diaphragm until the right atrium (**Figure 1(a)**). Bilateral pleural effusions and multiple lung nodules were also detected from the CT scan.

The patient was then diagnosed with HCC Barcelona Clinic Liver Cancer (BCLC) stage C. A bone marrow biopsy examination was performed and confirmed the presence of polycythemia with hypercellularity of bone marrow (**Figure 2(a), 2(b)**). From the biopsy findings, increased megakaryocytes with normal morphology were also observed (**Figure 2(c)**). From reticulin staining, there was no increased reticulin fibers from the findings (**Figure 2(d)**). No presence of somatic mutation of the Janus Kinase 2 (JAK-2) gene.

The main focus of the initial treatment was to manage the oncological emergencies,

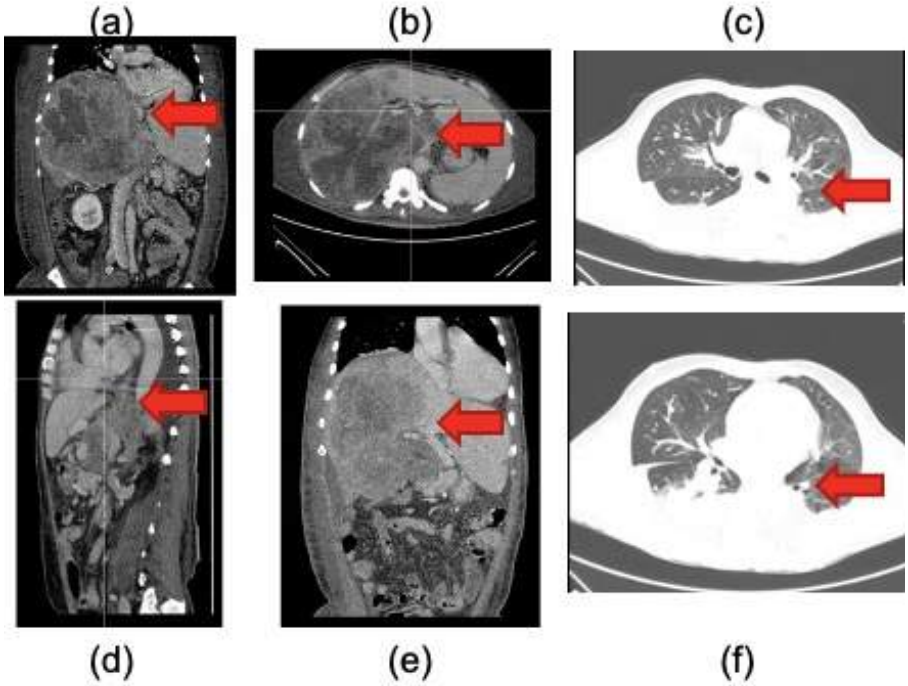

Figure 1. Radiographic findings from upper abdominal multiphasic CT-scan demonstrated a large hepatic lesion [(a), (b)] with the involvement of portal vein [(d), (e)] and extrahepatic manifestation [(c), (f)].

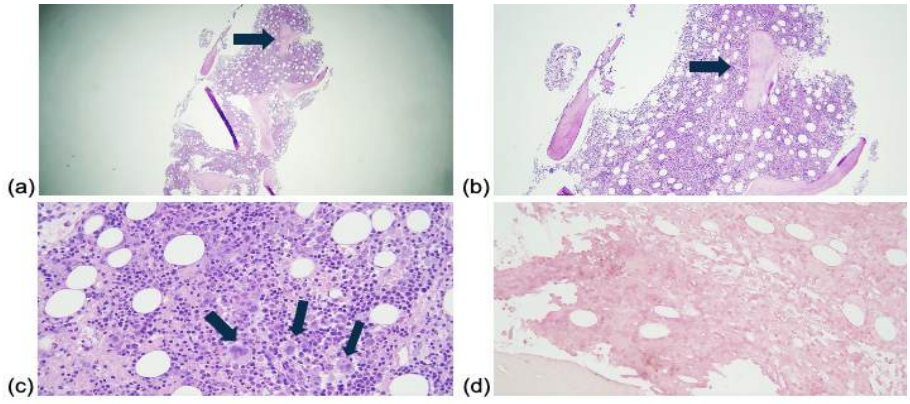

Figure 2. Histopathological examination with hematoxylin-eosin staining showed bone marrow hypercellularity ((a) and (b)) and increased megakaryocytes with normal morphology (c). No appearance of increased reticulin fibers was observed from reticulin staining (d).

i.e., polycythemia with the evidence of metastatic thrombosis in addition to recurrent hypoglycemia. We performed serial phlebotomy (twice a week), together with adequate hydration, initial administration of 50 ml of dextrose 40% intravenously, and maintained with dextrose 10% to a target level of at least 70 mg/dl of random blood glucose. Despite having received additional complex carbohydrates in his diet, hypoglycemic episodes still recurred; thus, parenteral administration of dextrose was continued until the end of his hospitalization. The patient also received cytoreductive agents in the form of hydroxyurea, as well as antiplatelet therapy (80 mg of acetylsalicylic acid daily per oral). **Figure 3** shows the clinical response after serial phlebotomy and oral cytoreduction treatment. Due to the advanced stage of the disease and the poor clinical condition of the patient, he was not a candidate for surgical therapy. However, the administration of oral multi-kinase inhibitors as one of the available systemic therapies for HCC in Indonesia was considered along with nucleoside and nucleotide analog as antiviral therapy. Unfortunately, both plans were never been implemented because the patient passed away due to severe hospital-acquired pneumonia.

DISCUSSION

Polycythemia and hypoglycemia are two paraneoplastic phenomena that can be found in HCC patients. Erythrocytosis or polycythemia cases are more uncommonly found in HCC patients compared to recurrent hypoglycemia. Nevertheless, previous studies in the African population found that the incidence of polycythemia in HCC patients ranged from 1% to 15.6%. In these studies, however, several confounding factors were noticed, such as the geographical locations of the subjects, where almost all of them were located in areas with an altitude of 1,750 meters above sea level. Another important confounding factor was a prominent delay in diagnosing HCC. Consequently, there might be some subjects who demonstrated normal or low hemoglobin levels attributed to anemia of chronic disease, while actually, they might exhibit polycythemia manifestation before the diagnosis of HCC.[4,6] An epidemiological study involving 792 HCC patients in China demonstrated that the prevalence of polycythemia was approximately 2%-5%.[7] On the other hand, the incidence of paraneoplastic hypoglycemia in HCC patients is more frequently found, with the incidence reaching as high as 24% in South America and 40% in Hong Kong.[4,8] More data from more recent epidemiological studies found that the prevalence of polycythemia was 3.9% in 457 HCC patients,[9] while the incidence of persistent hypoglycemia was 28.9% in 232 HCC patients.[10] A systematic review also pointed out that the estimated blood glucose level of HCC patients when they were first diagnosed was 30.8±12.2 mg/dl. This study also found that early manifestations related to hypoglycemia in these patients were significant dizziness (44.4%), nausea and/or abdominal pain (22.2%), and weight loss (27.8%).[11] All those findings were in line with the clinical manifestation and laboratory findings of our patient in this report.

Polycythemia or erythrocytosis is a paraneoplastic syndrome in HCC which can be attributed to increased production of erythropoietin by tumor cells. Generally, polycythemia can be classified into absolute and

	April 5th, 2022	April 6th, 2022	April 7th, 2022	April 9th, 2022	April 11th, 2022	April 13th, 2022
Hb	20.5	19.7	18.8	18.5	19	19.5
Ht	65.8	63.1	65	31	59.9	62.6
Platelets	234,000	213,000	182,000	148,000	142,000	130,000

Figure 3. Follow-up of laboratory examinations after serial phlebotomy and administration of cytoreductive agent had been conducted.

relative polycythemia. Absolute polycythemia consists of primary polycythemia (e.g., polycythemia vera), tumor-related secondary polycythemia (e.g., HCC, renal tumors), and hypoxia-related polycythemia (e.g., polycythemia found in patients with chronic obstructive pulmonary disease). Meanwhile, relative polycythemia occurs due to any conditions that may cause depleted plasma volume or body fluid volume, such as dehydration.[12,13] In the pathophysiology of HCC, synthesis and secretion of abnormal erythropoietin by tumor cells occurred by involving modified or naïve erythropoietin.[4] Another proposed mechanism of HCC-related polycythemia is a reduction of alpha-ketoglutarate and propyldehydroxilase levels in the tumor cells. As a result, there will also be a disruption in the signal transduction pathway of Hypoxia-inducible Factor-1-alpha (HIF-1-alpha), which leads to excessive production of erythropoietin. When erythropoietin binds to its receptors, a cascade of JAK-2 signal transduction pathways will be activated. Consequently, proliferation, stabilization, and differentiation of red blood cells will arise.[12,14]

In this case report, diagnosis of secondary polycythemia related to HCC BCLC stage C was considered due to the presence of increased hemoglobin level higher than 18.5 g/dl, accompanied by myeloproliferative appearance from peripheral blood smear examination and bone marrow hypercellularity from histopathological findings without any evidence of JAK2 exon 12 mutation. The clinical and laboratory findings in our patient were in line with the presence of secondary polycythemia, which might be attributed to higher synthesis and secretion of abnormal erythropoietin by a large number of tumor cells, indicated by large tumor volume and high serum AFP level. Relative polycythemia due to blood hyper-viscosity, either associated with increased red blood mass or malignancy-related hypercoagulability, was initially considered as an underlying mechanism in our patient. However, despite being adequately hydrated, the patient only demonstrated a good clinical response after serial phlebotomy and oral cytoreduction treatment; thus, diminishing the possibility of relative polycythemia condition.

In this patient, serial phlebotomy and administration of cytoreductive agents were conducted to treat secondary polycythemia. A population-based study performed on subjects with high-risk secondary polycythemia in South Korea exhibited the benefits of serial phlebotomy with a 2-week interval at most to significantly lower hematocrit level and thrombosis events.[15] Another study by Podoltsev, et al. in 2018 showed that more frequent serial phlebotomy accompanied by a higher proportion of days covered with hydroxyurea significantly improved the survival rate of patients with polycythemia vera and high risk of thrombosis.[16] Regardless, it is undeniable that peripheral blood tap also needs to be drawn periodically to monitor the therapeutic effect of recurrent phlebotomy; thus, at the same time, escalating the risk of iron deficiency which may also increase the blood viscosity. When 500 ml of blood is drawn, it is estimated that serum iron level could decrease 200-250 mg and serum ferritin level could decrease up to 44%.[12]

In our patient, initially, improvement of clinical symptoms and laboratory findings related to polycythemia had been observed. To minimize the risk of thrombotic events, our therapeutic aim is to maintain the hematocrit levels at a maximum of 45%. However, the hematocrit levels tended to increase again, even after the addition of cytoreductive agents. A retrospective study conducted by Mao, et al. showed a similar experience, in which phlebotomized patients had higher hemoglobin and hematocrit levels in comparison to the patients who did not undergo serial phlebotomy. The study also did not find any significant difference between the prevalence of arterial, venous, or total thrombosis before and after serial phlebotomy in secondary polycythemia cases.[17] In contrast, a case report by Fuqua, et al. demonstrated successful use of serial therapeutic phlebotomy in severe secondary polycythemia due to chronic lung disease. It is important to note, though, that the authors also successfully treated the main etiology of secondary polycythemia in the patient, which is chronic hypoxia, by administering adequate supplemental oxygen to the tissue.[18] In our assessment, secondary polycythemia condition

in our patient was strongly associated with HCC, therefore, the mainstay treatment is by administering a systemic therapy for advanced HCC, which had not been able to be implemented. Taken together, although there is still a paucity of high-quality evidence for evaluating the risk and benefit of routine phlebotomy in secondary polycythemia, clinicians should be aware that a definitive therapy for the underlying diseases still needs to be performed despite good initial clinical response after routine phlebotomy and administration of the cytoreductive agent.

In patients with a high risk of thrombosis, including our patient in this report, the administration of low-dose acetylsalicylic acid (ASA) (80-100 mg daily) with or without cytoreductive agents (e.g., hydroxyurea) is still recommended.[13,19] The anti-thrombotic properties of ASA itself are mainly attributed to impaired platelet activation due to the inhibition of thromboxane A_2 and acetylation of COX-1.[20] Another promising mechanism of ASA in HCC is the anti-tumor effect by decreasing the expression of collagen prolyl 4-hydroxylase A subunit 2, controlling glucose uptake through the NF-kB/GLUT1 axis, suppression of hepatocyte growth factor-induced invasion of HCC cells, and ASA-mediated immune-metabolic response through the modulation of the peroxisome proliferator-activated receptor delta-AMPK-peroxisome proliferator-activated receptor gamma coactivator 1-alpha axis.[21] A pooled analysis of two national-based cohort studies confirmed these theories by showing that increasing the cumulative mean dose of ASA can reduce the risk of HCC.[22] Nonetheless, one case report in a patient with HCC BCLC B and secondary polycythemia highlighted the fact that life-threatening cardiovascular complications may still develop despite routine administration of low-dose ASA.[12]

Although many benefits have been proven to be yielded from administering ASA, the possible risk of bleeding may require further anticipation. Around 0.4% to 20% of patients with advanced and invasive HCC have been shown to exhibit gastrointestinal metastasis. Additionally, 10% of cancer-related deaths in HCC were due to gastrointestinal bleeding.[23] Due to its anti-platelet activity, administration of ASA, even with low-dose, has been associated with an elevated risk of bleeding, especially in combination with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), clopidogrel, and Selective Serotonin Re-uptake Inhibitors (SSRIs).[24] Regardless, a recent meta-analysis by Wang, et al. demonstrated that utilization of ASA did not increase the risk of bleeding in patients with HCC (OR 1.19). In contrast, their subgroup analysis also demonstrated a risk reduction of liver cancer after administration of ASA by as high as 47%.[25] In line with the findings of Wang, et al., our patient in this case report also did not exhibit any clinical manifestation of gastrointestinal tract bleeding throughout his course of treatment with ASA. Our case was in line with studies favoring the use of ASA, in which, no new onset of thrombosis was observed throughout his hospitalization.

As has been explained in this case, another dilemma that can be encountered in the management of secondary polycythemia is the use of cytoreductive in the presence of severe infection. A previous database study by Polverelli, et al. demonstrated a slightly higher number of infectious complications in myelofibrosis patients who received cytoreductive therapy (78%) compared to the control group.[26] Conflicting evidence, however, emerged from a study comparing ruxolitinib and standard therapy, which included hydroxyurea, in patients with polycythemia vera. This study showed a lower rate of infections in groups treated with hydroxyurea (36.9%), in comparison to groups treated with ruxolitinib (41.8%).[27] A possible reason behind this is that the administration of a cytoreductive agent does not necessarily cause immune suppression. As a cytoreductive agent, hydroxyurea displays its cytostatic effect through the inhibition of ribonucleoside diphosphate reductase, which catalyzes the conversion of ribonucleotides to deoxyribonucleotides; thus, arresting the cell cycles between G1 and S phases or in early S phase. This step, nonetheless, does not significantly affect the T-lymphocyte's immunological functionality. Instead, increased T-helper type 1 and type 2 cytokine production was found upon treatment with hydroxyurea.[28]

Based on the onset, etiology, and

pathophysiology, persistent hypoglycemia in HCC can be grouped into two types. Type A hypoglycemia is mild-to-moderate hypoglycemia, which is usually observed in advanced HCC, particularly in a large-sized progressive tumor. Enlarged tumor cells, exceeding the normal size of the liver, will diminish the capability of liver cells to perform gluconeogenesis and glycogenolysis optimally, while at the same time, the requirement of glucose will also be increased as tumor size is getting larger, contributing to higher direct consumption of glucose by tumor cells. Meanwhile, type B hypoglycemia, which is usually found in 5%-13% of HCC patients, tends to have the more severe manifestation of hypoglycemia in the early phase of malignancy. The mechanism of type B hypoglycemia is thought to be associated with the production of partially processed Insulin Growth Factor/ IGF-2 molecules. In this case report, the patient was thought to exhibit manifestation of type A hypoglycemia due to the most recent radiographic examinations, which showed an extension of liver mass with hardly observed normal remnants of liver parenchyma, indicating enlarged progressive mass.[11] Our patient also exhibited recurrent hypoglycemia without any increase in basal insulin level. Normal basal insulin level, along with the absence of any radiographic findings showing an islet cell tumor, further confirmed the diagnosis of non-islet cell tumor hypoglycemia in our patient.

Aside from excessive glucose utilization by tumor cells, secretion of partially processed molecules, such as IGF-2, can also disturb glucose metabolism, resulting in persistent HCC-related hypoglycemia.[29-31] A report on one HCC patient with the presence of liver cirrhosis due to alcoholic liver disease and persistent hypoglycemia showed a high IGF-2 level until almost twofold of its normal limit. In HCC, higher IGF-2 is strongly affected by higher pro-IGF-2, which was caused by the reduced ability of pro-IGF-2 to bind with Insulin-like Growth Factor Binding Protein (IGFBP)-3. This cascade of events will stimulate insulin receptors continuously, leading to suppression of free fatty acids release, as well as inhibition of gluconeogenesis, glycogenolysis, and ketogenesis of the liver. Therefore, hypoglycemia events will be more severe in HCC patients.[31]

In this report, we also highlighted an example of an advanced HCC case with a less than favorable prognosis, which can be predicted since the initial hospital admission of the patient. Even without the presence of tumor-related complications, a higher BCLC stage has been identified as a significant risk factor for a higher mortality rate in an Indonesian cohort retrospective study.[32] Previous evidence in 196 subjects also pointed out that HCC BCLC C patients who did not receive any systemic therapy only had short median survival (56 days) with the most common cause of death being tumor-related progression (50%) and secondary infection (21.7%).[33] In our patient, systemic therapy became the best therapeutic option due to the presence of vascular invasion, i.e., portal vein thrombosis, and extrahepatic spread.[34] Following the previous findings from Jasirwan, et al.[32] and Hasan, et al.[33], our patient was also presented with BCLC stage C upon admission and eventually passed away due to secondary pulmonary infection before he was able to get any systemic therapy. Both studies above also demonstrated the fact that hepatitis B was still the most common etiology of HCC (63.1%-69.4%) in Indonesia.[32,33] History of untreated hepatitis B, which led to lack of surveillance and follow-up, was the most prominent contributing factor to diagnostic delay in our patient.

The presence of paraneoplastic polycythemia may also worsen the prognosis of our patient. Miao, et al. and Ke, et al. revealed that a worse prognosis in HCC patients with polycythemia was significantly associated with larger tumor size, higher AFP levels, and mutations of genes that have a role in oxidative phosphorylation of mitochondria. This study also showed that erythropoietin has a direct role in tumor progression through signal transduction JAK/ STAT pathway.[14,35] Aside from those things, difficulty in treating polycythemia also becomes a problem behind poorer prognosis of the patients. Another case report exhibited evidence that a combination of phlebotomy, trans-arterial chemoembolization, and administration of low-dose aspirin did not decrease the risk of

cardiovascular-related mortality in HCC BCLC stage B patients.[12] Another study by Evers, et al. in 2014 also highlighted the possibility of utilizing therapeutic erythrocytapheresis as a treatment option for secondary polycythemia. Evers, et al. demonstrated that in comparison to phlebotomy, the group treated with erythrocytapheresis had a more significant decrease in red blood cell volume and needed longer intervals between procedures.[36]

Concurrently, the poorer prognosis of HCC patients with recurrent hypoglycemia has been strongly associated with hypoglycemia-related emergencies and a lack of good clinical response toward conventional hypoglycemia treatment. In patients with severe persistent hypoglycemia, administration of intravenous glucose and/or carbohydrate intake as high as 1,500 grams daily often did not show adequate results in maintaining blood glucose levels. Further available evidence also showed that administration of steroids, glucagon, and growth hormones did not have any significant therapeutic impact on HCC-related persistent hypoglycemia. Until now, the best definitive therapeutic option for HCC-related hypoglycemia is cytoreductive options, such as surgery, radiotherapy, and/or systemic therapy.[28,29]

CONCLUSION

Polycythemia and persistent hypoglycemia are paraneoplastic phenomena that can be found in HCC patients. Elevated risk of blood hyperviscosity and polycythemia-related thrombosis, as well as medical emergencies attributed to autonomic and neuroglycopenic manifestations of hypoglycemia, highlight the importance of close monitoring and prompt treatment of both conditions. Aside from escalated tumor burden, both phenomena occur more often in patients with advanced HCC; thus, limiting the availability of therapeutic options, in particular the curative strategies. As a result, lower survival of these patients may also be observed. This case also emphasized the importance of performing a national surveillance program appropriately for early detection of HCC in high-risk patients, particularly patients with chronic hepatitis B. Continuously increasing incidence of hepatitis B in Indonesia, which may also be untreated or underdiagnosed, has been proven to be a significant risk factor in HCC-related morbidity and mortality. Therefore, early diagnosis and prompt treatment of hepatitis B are also strongly recommended as preventive strategies for HCC and its complications.

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Unusual Presentation of Unilateral Choroidal Melanoma with Bilateral Vasculitis in Young Individual: A Case Report and Review of Literature

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ABSTRACT

Ocular melanoma stands as the predominant primary intraocular malignancy, albeit infrequently exhibiting ipsilateral inflammatory manifestations. In this article, we present an exceptional case involving a middle-aged male who presented with unilateral ocular choroidal melanoma alongside bilateral retinal vasculitis. The patient initially received temporary steroid treatment, followed by brachytherapy, which contributed to the resolution of vasculitis symptoms. The study aims to document the atypical occurrence of bilateral retinal vasculitis, which could potentially masquerade as melanoma, emphasizing the need for heightened vigilance and further investigations when encountering choroidal masses in its presence. Future research endeavors are warranted to better understand the incidence of such occurrences in this context.

Keywords*: Melanoma, Vasculitis, Uveal Melanoma, Choroidal Melanoma, Macular Lesion, Uveitis, Ocular melanoma, masquerade.*

INTRODUCTION

Uveal melanoma is the most common primary intraocular malignancy.[1] There are approximately 7095 new cases of uveal melanoma annually, over half of this number in white non-Hispanic populations. This incidence has been stable over a decade.[2] Choroidal melanoma, especially the small lesions, can be difficult to diagnose initially due to the wide variety of mimickers. Diagnosis of choroidal melanoma is usually reached with the aid of ancillary tests including imaging, in addition to the use of indirect ophthalmoscopy.

A masquerade syndrome is an ophthalmological entity where a neoplasm mimics an inflammatory condition. Ocular melanoma may rarely present with ipsilateral inflammatory signs or vitreous hemorrhage and has most frequently been noted in those with tumor necrosis and mixed or epithelioid cell types.[3,4] In this case, we present an unusual case of unilateral macular choroidal melanoma with bilateral vasculitis in a middle-aged patient.

CASE ILLUSTRATION

This is a case of a 37-year-old Saudi male patient, medically free, who presented to the emergency department at Dhahran Eye Specialist Hospital (DESH) complaining of distorted central vision, in the form of metamorphopsia, with minimal decrease of vision of the left eye throughout a couple of months. There was no associated history of trauma, headache, nausea, vomiting, flashes of light, fever, weight loss, night sweating, neck pain, joint pain, or rashes. There was a positive history of left Ramsay Hunt syndrome (*herpes zoster oticus*), which

was treated with steroids and resolved without residual complications. The past ocular, surgical, and family histories were unremarkable. The patient provided a positive history of smoking.

On examination, the visual acuity and intraocular pressure were 20/20 and 20/50, 19 mm Hg and 17 mm Hg in the right and left eyes, respectively. The anterior segment examination was within normal limits in both eyes. Dilated fundus examination, (**Figure 1**), showing the left eye with a pigmented choroidal lesion under the macula with overlying orange pigmentation demonstrated hyperautofluorescence on Fundus Autofluorescence and perivascular sheathing in the periphery in both eyes.

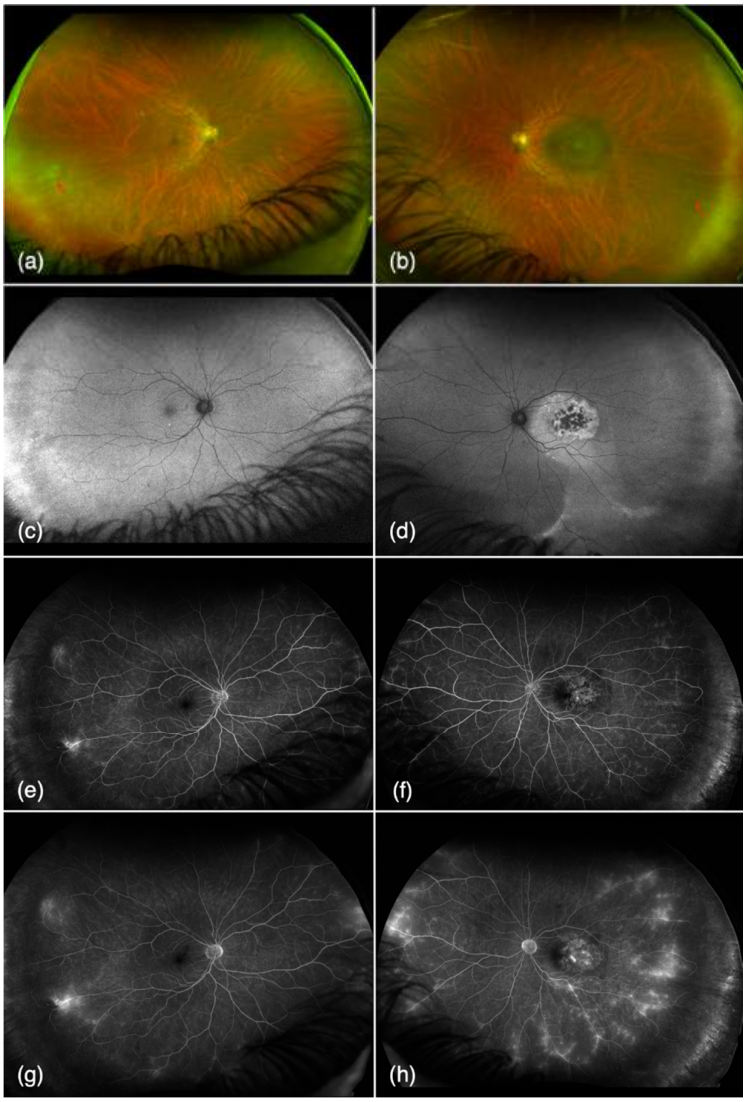

Figure 1. (a,b) Color Fundus Photo of both eyes showing (left eye) with pigmented choroidal lesion under the macula with overlying orange pigmentation and areas of peripheral retinal vasculitis 'red arrows'. (c,d) Fundus Autofluorescence Photo showing hyperautofluorescence of the choroidal lesion (left eye). (e.f) Fundus fluorescein angiography early frames showed patches of hypo and hyperfluorescence in the macula of the left eye, and the peripheries of both eyes showed diffuse capillary leakage with vasculitis. (g,h) late frame Fundus fluorescein angiography photos showing staining and leakage of the mass in the left eye with bilateral peripheral diffuse leakage and staining of the blood vessels which is more in the left eye.

Fundus fluorescein angiography showed patches of hypo and hyperfluorescence in the macula of the left eye. The retinal periphery of both eyes showed diffuse capillary leakage with vasculitis in retinal venules and capillary nonperfusion in late frames (**Figure 1**). B-Scan showed a choroidal lesion sized 7.06*8.54 mm and 3.17 mm thickness with low to medium internal reflectivity (**Figure 2**). Optical Coherence Tomography, (**Figure 3**), showed a choroidal large mass with subretinal fluid and hyperreflective subretinal (lipofuscin) deposits.

Complete blood count with differential (CBC), Liver function tests (LFTs), and Renal function tests all were within normal limits. The most common infectious etiology was ruled out as we found out that Tuberculin skin (TST) or purified-protein derivative (PPD) was negative, The rapid plasma reagin (RPR) test was negative and Toxoplasma latex was negative. ANA (Antinuclear Antibody) Test was positive. The patient was unlikely to have sarcoidosis as the Angiotensin Converting Enzyme (Blood) was within normal limits as well. Magnetic resonance

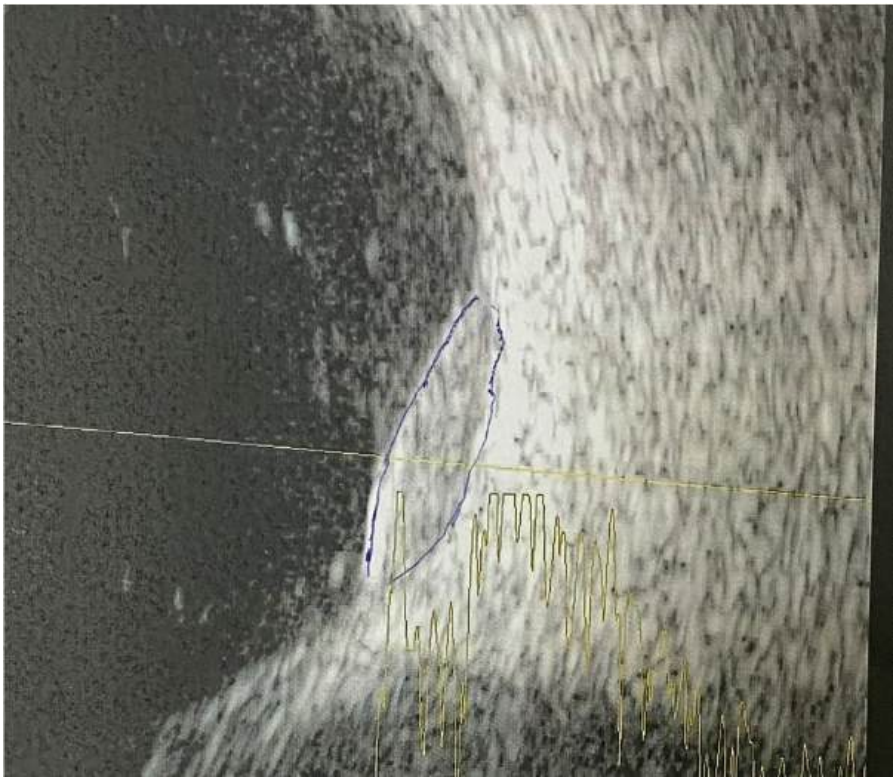

Figure 2. B-scan ultrasonography of the left eye showing choroidal mass with low to medium internal reflectivity.

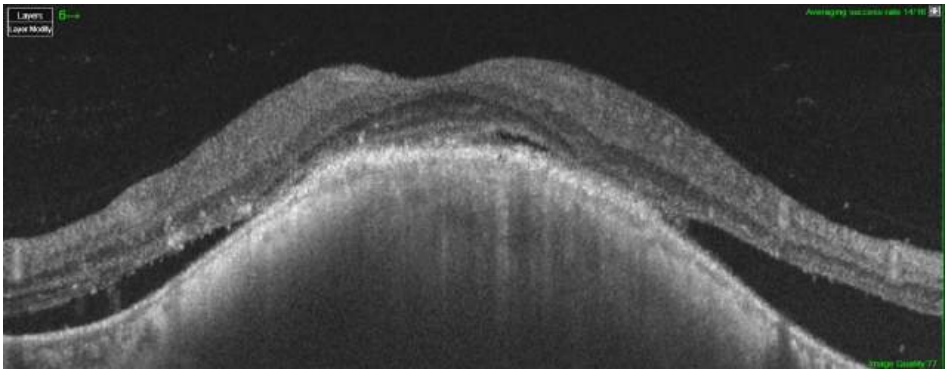

Figure 3. Optical Coherence Tomography showing large choroidal mass with subretinal fluid and hyperreflective subretinal (lipofuscin) deposits.

imaging (MRI) of the brain and spine was done as well as a computerized tomography (CT) scan of chest, abdomen, and pelvis done with no signs of malignancy or any other abnormalities.

The case was diagnosed as a left-eye choroidal melanoma with bilateral ocular paraneoplastic inflammation in the form of vasculitis. The patient was treated with oral prednisolone 60 mg daily tapering weekly by 5 mg for the vasculitis, and the patient was referred for plaque brachytherapy with close serial follow-up.

Before the brachytherapy in the serial follow-up, the mass documented an increase in size in the b-scan which reached a thickness of 4.8 mm, but the vasculitis was controlled on the oral prednisolone. (**Figure 4**)

After the brachytherapy, the patient's visual acuity dropped to 20/400 and he showed a decrease in the size of the mass in serial follow-ups documented by the b-scan, which reached 2.96 mm thickness with omit radiation retinopathy surrounding the area of the mass corresponding to the area of the brachytherapy as well as regression of vasculitis despite the stoppage of oral prednisolone as seen in (**Figure 4**). The patient was planned to regularly visit the clinic and he will be managed accordingly if there are any signs of inflammation or regrowth.

DISCUSSION

Uveal melanoma is the most common primary intraocular tumor with an incidence of 4 to 5 cases per year in the United States and slightly higher in Europe.[5,6] The majority of uveal melanoma patients are between 50 to 80 years of age. Multiple factors play a role in the pathogenesis of uveal melanoma including ethnicity and multiple intrinsic predisposing factors like lighter color of skin and conditions like oculodermal melanosis.[7] However, in this case, the patient was young and of Middle Eastern ethnicity, which we think contributed to the atypical presentation with bilateral vasculitis because a younger patient has a stronger immune system.[8]

To the best of our knowledge, this case is the second macular choroidal melanoma reported with bilateral vasculitis in the literature. The only similar previous case was reported in 1995 by Steel et al,[4] concerning a young male patient with left anterior unilateral choroidal melanoma and bilateral retinal vasculitis. In contrast to our case, the oral corticosteroid did

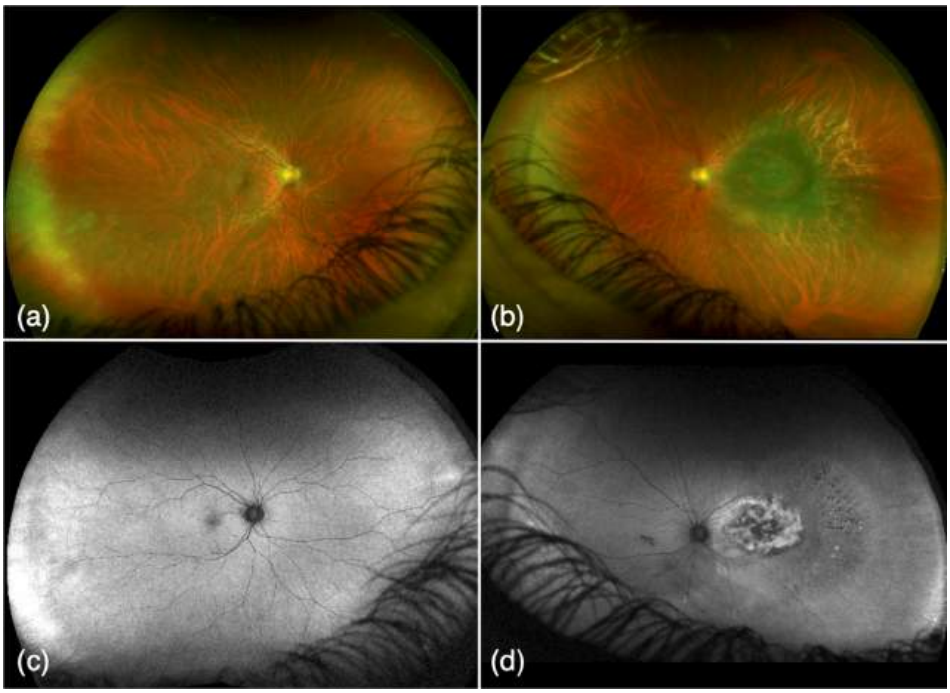

Figure 4. (a,b) Color Fundus Photo of both eyes showing (left eye) with pigmented choroidal lesion under the macula with areas of omit radiation retinopathy surrounding the mass. (c,d) Fundus Autofluorescence Photo showing hyperautofluorescence of the choroidal lesion (left eye).

not affect the retinal vasculitis in their case, but it decreased dramatically after the patient underwent enucleation. That was supported by the finding in our patient who had resolved vasculitis after brachytherapy and the shrinkage of the melanoma size despite the stoppage in oral corticosteroids.

Pathogenesis of bilateral vasculitis is unknown in both cases. However, it is speculated that there is a cross-reactivity between the melanoma and various retinal antigens resulting in altered antiretinal autoimmunity and subsequent retinal vasculitis.[4] This was reinforced by the fact that vasculitis has improved after enucleation in their patient. On the other hand, the association of unilateral uveitis with uveal melanoma is not infrequent. These cases are usually masquerading as panuveitis and are associated with anterior choroidal melanoma or tumor necrosis.[9] Sympathetic ophthalmia is also known as secondary to necrotic choroidal melanomas, often with extraskeletal extension.[10]

CONCLUSION

This article presents a noteworthy instance of choroidal melanoma accompanied by bilateral vasculitis. This report underscores the concealment potential of masquerade syndrome and intraocular hemorrhage for neoplastic origins, with uveal melanoma emerging as the predominant primary intraocular malignancy. Particularly in the context of small lesions, the diagnostic challenge arises from the diverse array of conditions that can mimic choroidal melanoma. When confronted with bilateral intraocular vasculitis and suspected neoplastic pathology, a heightened consideration for biopsy becomes imperative to ensure an accurate diagnosis. Further investigations are warranted to elucidate the association of bilateral vasculitis as an indicative marker of melanoma and to assess its overall incidence within this context.

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Insulin Use and The Risk of Hepatocellular Carcinoma: Insights and Implications

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ABSTRACT

In recent years, the incidence of diabetes mellitus and hepatocellular carcinoma (HCC) has been increasing worldwide, in the context of an increasing prevalence of non-alcoholic fatty liver disease (NAFLD). In patients with diabetes mellitus, exogenous insulin is commonly prescribed and used in long-term settings. Recent studies suggest that insulin use may elevate the risk of HCC. A substantial body of work seeks to unpack the association between insulin use and the risk of developing HCC, although there may be conflicting evidence. Further validation is necessary to clarify the true relationship between insulin mechanisms and its hepatocarcinogenic effect. Given the burden of diabetic patients developing HCC, diabetologists and hepatologists must collaborate, particularly regarding the prevention and surveillance of HCC in diabetic patients.

Keywords*: hepatocellular carcinoma, insulin, insulin use, risk.*

INTRODUCTION

Liver cancers are the fourth most common cause of cancer-related death and rank sixth in terms of incident cases worldwide. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers. In most countries, Hepatitis B or C virus (HBV or HCV) infection and alcohol abuse are widely recognized as the major etiology of HCC.[1] However, in recent years, the increased prevalence of non-alcoholic fatty liver disease (NAFLD), including type 2 diabetes mellitus, amplifies the risk of liver cancer. Consequently, NAFLD soon may become a leading cause of liver cancer in the future.[2]

Several studies have established that type 2 diabetes mellitus is associated with an increased risk of HCC. In a meta-analysis, type 2 diabetes mellitus was at a 2.3-fold risk of developing HCC, which accounts for the highest risk among the 20 cancer types included in the study.[3] In a case-control observational study, diabetes is associated with more advanced lesions and poorer long-term prognosis in HCC patients.[4]

Given the increased risk of HCC in patients with diabetes, it has been suggested that anti-diabetic medication use could modify the risk. Although data on the role of anti-diabetic medication in HCC are limited, there is an indication that insulin use may increase the risk.[5] In patients with HbA1C > 9% or patients who failed to achieve their blood glucose target after being given the optimal dose of a combination of oral anti-diabetic medications, insulin is widely prescribed and often used in a long-term setting.[6] Thus, decisions concerning insulin prescribing and understanding the risk of developing HCC are substantial. Therefore, the purpose of this review is to examine the use of insulin and

its association with increased risk of HCC in diabetic patients. This review intends to inform future research and serve as a basis for potential study designs.

PHYSIOLOGICAL INSULIN SIGNALING PATHWAY

Insulin is a major anabolic hormone produced by the islet cells of the pancreas primarily for glycemia elevations. In the liver, insulin acts on hepatocytes to inhibit gluconeogenesis and stimulate glycolysis, glucose storage as glycogen, protein synthesis, and lipogenesis. Apart from its metabolic effects, insulin is also a prominent growth factor for hepatocyte division and survival.[7]

Insulin binds to insulin receptors (IR), which are expressed in all cell types in the body. IR activates its tyrosine kinase and initiates a series of signaling pathways such as Ras-MAPK, PI3K-Akt, and mTOR.[8,9] The insulin receptor substrates (IRS), acting as adaptor proteins, recruit various signaling complexes.[10] Notably, growth factor receptor-bound protein 2 (Grb2) is recruited to the binding site on IRS and phosphorylates Ras. This leads to the activation of Ras and subsequently activates the mitogen-activated protein kinase (MAPK) signaling cascade.[9] Rac1, a member of the GTPase superfamily, plays a crucial role in insulin-induced glucose uptake and glucose-induced insulin secretion.[11] IRS proteins also interact with the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K), which in turn controls the activation of Akt through phosphoinositide-dependent kinase 1 (PDK1). The activation of Akt is vital for regulating metabolic enzymes, as well as facilitating cell proliferation and survival.[12] Additionally, the PI3K-Akt pathway regulates the mammalian target of the rapamycin (mTOR) pathway, which plays a central role in cell growth and metabolism.[13]

Insulin-like growth factors (IGF) are a part of the insulin-related family. These compounds (IGF-1 and IGF-2) share homologous structures with insulin although they have different origins. The production of IGF-1 is controlled mostly by the action of growth hormone in the liver. IGF is functionally related to insulin but has a much higher growth-promoting activity. Both IGFs and insulin act as ligands for their respective receptor tyrosine kinases—the IR and the insulin-like growth factor 1 receptor (IGF-1R).[8] The IR and IGF-1R are highly similar and share many overlapping signaling pathways. Activation of both receptors leads to stimulation of the major canonical signaling pathways: Ras-MAPK, PI3K-Akt, and mTOR. Disruptions in these pathways can lead to insulin resistance, which is characterized by glucose intolerance, dyslipidemia, and elevated risk of cardiovascular disease or alterations in growth.[8,14]

DIABETES MELLITUS, INSULIN, AND HEPATOCELLULAR CARCINOMA

The relationship between insulin mechanisms and its hepatocarcinogenic effects is inseparable from the underlying mechanisms of diabetes mellitus and chronic liver disease **(Figure 1)**. In patients with cirrhosis-related diabetes mellitus, insulin has a decreased ability to suppress hepatic gluconeogenesis, and hepatic insulin degradation is impaired. These mechanisms promote hyperinsulinemia, which initially compensates for insulin resistance, but eventually leads to hyperglycemia. Moreover, cirrhosis itself reduces the functional mass of hepatocytes and results in portosystemic shunting.[15]

Given that insulin resistance is a prominent characteristic of chronic liver disease that is predisposed to HCC, there is a belief that the activation of the insulin pathway due to hyperinsulinemia leads to the development of liver carcinogenesis. One possible hypothesis is that hepatic insulin resistance is partial, allowing certain pathways to retain sensitivity to higher-than-normal insulin levels. During chronic liver disease, hepatocytes that have evaded apoptosis and necrosis face significant selection pressure from factors such as inflammation, hyperglycemia, oxidative stress, and elevated levels of circulating free fatty acids, which likely contribute to cellular transformation to carcinoma cells.[15]

Ultimately, several mechanisms including hyperinsulinemia, insulin resistance, or exogenous insulin treatment, have been suggested

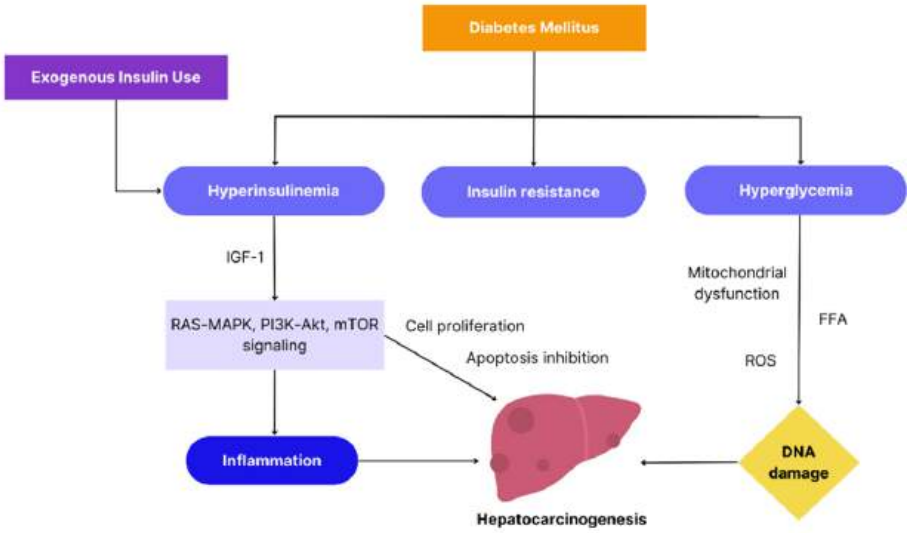

Figure 1. Pathogenic pathways that may link diabetes mellitus and insulin use to HCC development.

to explain the association between diabetes and HCC. An increase in circulating insulin levels is also seen in patients treated with exogenous insulin. Indeed, in an experimental study, exogenous insulin injection promotes colonic carcinogenesis in rats.[16] Similarly, patients with type 2 diabetes exposed to exogenous insulin have a significantly increased risk of cancer-related mortality.[17]

Insulin could be directly related to risk by promoting tumor proliferation, or it could affect risk by modulating circulating levels of growth factors and their binding proteins or by competing with their specific receptors in target tissues.[18] The insulin receptor (IR) is significantly overexpressed in 40% of the analyzed HCC tumors compared to the surrounding non-tumor tissue.[19] This overexpression is accompanied by a significant change in the relative expression of IR isoforms in approximately 70% of HCC samples. The insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) are frequently overexpressed in HCC tumors compared to non-tumor liver tissue at both the mRNA and protein levels.[20,21] This overexpression is observed even in the early stages of liver carcinogenesis, where it can enhance insulin signaling. In patients with HCC, IRS-1 overexpression is associated with larger tumor size and tumor progression.[20] Moreover, insulin also activates the IGF-I receptor, known to have growth-promoting effects. Thus, reduced insulin sensitivity with compensatory hyperinsulinemia leads to an elevated level of IGF-I and stimulation of cell proliferation. The IGF-I could act as a growth stimulus in preneoplastic and neoplastic cells.[22]

STUDIES ON THE ASSOCIATION BETWEEN INSULIN USE AND RISK OF HCC IN DIABETIC PATIENTS

In the past decade, several studies have observed the elevated risk of HCC incidence in diabetic patients treated with insulin. In Shanghai, Gu et al conducted an observational cohort study in 8,774 insulin-naïve diabetes patients. The result showed that the risk of liver cancer was significantly higher in the insulin users compared to that in the non-insulin users (adjusted RR,2.84, 95% CI 1.12–7.17).[23] Similarly, a study by Kasmari also showed that insulin increased the risk of HCC compared with the general type 2 diabetes mellitus population (OR, 1.64, 95% CI 1.48-1.81).[24] Schlesinger et al conducted a prospective analysis involving 363,426 participants with self-reported diabetes. During 8.5 years of follow-up, 176 HCC cases were identified and the risk for HCC was particularly higher in participants treated with insulin (RR, 6.19, 95% CI 3.50-10.18).[25] Similar results were found by Bosetti et al, who analyzed the role of various antidiabetic drugs on HCC risk in a large population-based study from Italy. The

study reported that an increased risk of HCC was found with insulin use in diabetic patients (OR, 3.73; 95% CI, 2.52–5.51).[26] These findings were consistent with a meta-analysis by Singh et al, who found an increased risk of HCC in insulin users (OR, 2.61, 95% CI 1.46–4.65).[27]

The duration of insulin use was found to be associated with an increased risk of HCC. Bosetti et al demonstrated that the risk of HCC increased with a longer duration of insulin use (OR, 2.52 for <1 year, 5.41 for 1–2 years, and 6.01 for ≥2 years). These findings indicate that insulin plays a genuine role in the development of HCC, although the over two-fold excess risk observed for use for less than 1 year suggests that diabetic patients under insulin treatment have a higher background rate of HCC, probably related to their diabetes severity.[26]

Mannucci et al conducted a case-control study to analyze the doses of insulin and its analogs and cancer occurrence in type 2 diabetic patients. During a median follow-up of 75.9 months, 112 cancer cases were identified, including 18 hepato-gastrointestinal cancer. The study reported that incident cancer was associated with a dose of glargine ≥0.3 IU/kg/day (OR, 5.43, 95% CI 2.18–13.53). Given the possibility of an association between cancer and higher glargine doses, the study suggested that dosage should be taken into consideration when assessing the potential link between insulin and its analogs with cancer.[28]

Overall, although evidence suggests that insulin could increase the risk of HCC in diabetic patients, there may be some conflicting results from other studies **(Table 1)**. A retrospective

Table 1. Summary of clinical studies on the impact of insulin use on the risk of HCC.

Reference	Country	Study Design	Study Population	Results
Gu, et al.[23] (2013)	China	Population-based, observational cohort study	3,639 insulin-user patients, 5,135 the non-insulin user patients	Increased risks of liver cancer were found in insulin users, compared to that in the non-insulin users (adjusted RR,2.84, 95% CI 1.12–7.17)
Kasmari, et al.[24] (2017)	USA	Retrospective cohort study	2,095 diabetic and HCC patients, 5,022 diabetic patients without HCC	Insulin (OR, 1.640, 95% CI 1.48-1.81) increased the risk of HCC compared with the general type II diabetes population
Schlesinger, et al.[25] (2013)	Europe	Prospective cohort study	363,426 diabetic patients	The risk of HCC was particularly higher in patients treated with insulin (RR, 6.19, 95% CI 3.50-10.18)
Bosetti, et al.[26] (2015)	Italy	Nested case-control study	190 diabetic and HCC patients, 3,772 controls	Increased risks of HCC were found for the use of insulin (OR, 3.73, 95% CI 2.52-5.51)
Kawaguchi, et al.[35] (2010)	Japan	Nested case-control study	138 diabetic, Hepatitis C, and HCC patients, 103 controls	Use of insulin was a significant independent factor associated with HCC incident (OR, 2.969, CI 95% 1.293-6.819)
Singh, et al.[27] (2013)	USA	Meta-analysis of RCT and observational studies	334,307 patients with diabetes	Insulin use increased the risk of HCC (OR, 2.61, 95% CI 1.46-4.65)
Oliveria, et al.[29] (2008)	USA	Retrospective cohort study	191,223 patients with diabetes, 39 HCC cases	Exposure to insulin or other antidiabetic treatment was not associated with HCC risk
Simon, et al.[30] (2018)	USA	Prospective cohort study	10,110 diabetic patients, 112 HCC cases	In diabetic patients, insulin use was not significantly associated with HCC risk
Lai, et al.[31] (2012)	Taiwan	Retrospective cohort study	19,349 diabetic patients, 77,396 non-diabetic patients	There was no significant association between insulin and the risk of developing HCC
Kramer, et al.[36] (2022)	USA	Retrospective cohort study	85,963 patients with NAFLD and diabetes, 524 HCC cases	Insulin did not affect HCC risk, however, insulin in combination with other oral medications was associated with a 1.6 to 1.7-fold higher risk of HCC

cohort study among patients with type 2 diabetes was conducted using a large US population-based database. Among the 39 liver cancer cases found during follow-up, exposure to insulin and other antidiabetic regimens was not associated with an appreciable increase in HCC risk.[29] Furthermore, in a large cohort study with over 26 years of follow-up, there was a trend toward increased risk of HCC with insulin use, but this did not reach statistical significance.[30] In the Taiwanese study, there was no significant association between insulin and the risk of developing HCC.[31] The variations in findings between these studies and contradictory results reported in other studies could be attributed to differences in underlying population risk factors. In addition, the treatment duration and its impact on risk may influence the statistical analysis. However, rather than representing an association of HCC risk with the medication itself, this may serve as a marker of disease severity, as patients with more severe diabetes are typically treated with insulin.

FUTURE DIRECTIONS

Albeit further validation is needed to clarify the true relationship between insulin use and HCC risk, existing shreds of evidence suggest that insulin may have some hepatocarcinogenic effects. Considering the complex mechanism between HCC and insulin, and the burden of diabetic patients developing HCC, it is crucial to establish effective strategies for HCC surveillance in diabetic patients. The current national guidelines recommend HCC surveillance only for patients with cirrhosis or those with viral hepatitis.[32] Therefore, there is an urgent need for detecting HCC at a treatable stage in diabetic patients.

Adhering to the national guidelines, implementing routine HCC surveillance every six months through ultrasound examinations may be a reasonable approach.[32] Another method, transient elastography measurement, can be considered to evaluate liver stiffness in the population at risk. Additionally, since liver fibrosis is a major predictor of HCC in chronic liver disease, non-invasive fibrosis markers could be useful for risk stratification of HCC. Several studies have identified scoring systems to determine liver scarring and cirrhosis, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), AST-to-ALT ratio, NAFLD fibrosis score, and fibrosis-4 (FIB-4) index.[33] A national cohort study from Japan, recruited 239 patients with T2DM who were diagnosed with non-viral HCC, with 5 years of follow-up at diabetes clinics before HCC diagnosis. The study found that the FIB-4 index was an outstanding predictor of HCC development, with an AUROC of 0.811 for predicting the 5-year HCC incidence. This result suggests that a simple calculation of the FIB-4 index in diabetes clinics can be the first step for the surveillance of HCC with non-viral etiology. Hence, future prospective studies are needed to validate the efficacy of surveillance strategies based on non-invasive methods.[34]

CONCLUSION

Understanding the complex relationship between diabetes mellitus, insulin, and HCC is challenging due to the involvement of various signaling pathways in the disease progression. Clinical studies have indicated a higher risk of HCC in patients receiving insulin treatment. However, further investigation is required to determine the specific role of insulin use and its potential carcinogenic effects. Given insulin's widespread and long-term use, collaboration between diabetologists and hepatologists is crucial for studying liver diseases in diabetic patients. This collaboration is particularly important for conducting future research to gather evidence regarding the prevention and surveillance of HCC in diabetic patients.

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MPox Skin Lesions

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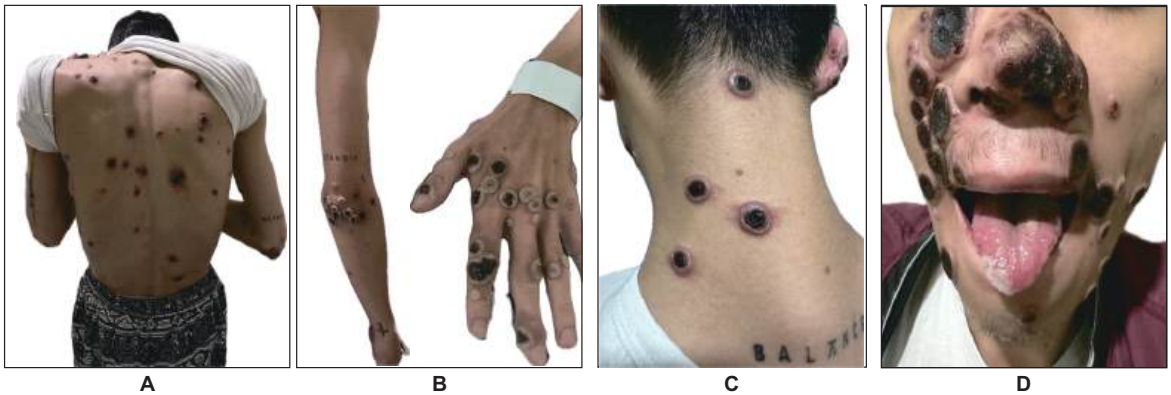
A B

Figure 1. (A-B) A 48-year-old male with Mpox and mild skin manifestation.



A B C D

Figure 2. (A-D) A 28-year-old male with Mpox and severe skin manifestations, involving mucosal surface.

The Monkeypox virus was first identified as a cause of disease in humans in the 1970s in the Democratic Republic of the Congo.[1] The first reported mpox case in Indonesia was in October 2022 which was identified as an imported case, there were no new confirmed mpox cases until 13 October 2023.[2]

Mpox is mostly found in patients who identify as men who have sex with men. High-risk sexual behaviors such as having multiple sexual partners were also considered as potential risk factors.[2] Approximately half of confirmed mpox cases were found in patients living with HIV.[1,2] Mpox usually causes systemic symptoms followed by skin lesions. The number of skin lesions in mpox can vary from a few up to 1.000 lesions in severe cases. The skin lesions may last for weeks and may involve several stages from small macules that evolve to papules, vesicles, and pseudo-pustules. The lesions are usually well-circumscribed and umbilication can be found.[1]

Patients with HIV may present with skin lesions caused by opportunistic infections, AIDS-specific skin eruptions, or antiretroviral therapy-associated drug eruptions.[1,3] The skin manifestation of mpox may be dismissed as other conditions, causing underdiagnosis in this at-risk population. A high degree of clinical suspicion for mpox is needed for patients with new onset skin lesions in patients that were in high-risk group.[2]

We present two different spectrums of mpox skin lesions in patients living with HIV, with a positive polymerase chain reaction test for mpox. The first patient is a 48-years-old male, who develops a maculo-papular lesion, that initially noticed on the face, the lesions were then spread to the back and hand. He identifies as men who have sex with men and living with HIV for the past 18 years. There were no lesions on the genitalia or mucosa. (**Figure 1A-B**). The second patient is a 28-years-old male, the initial symptom was fever, followed by skin lesions after around 1 week of fever. The lesion initially appears as pustules on the face and then spreads throughout the whole body, the lesions also grow larger in size and become pseudo-pustules and ulcers. There were also mucosal involvements in the mouth, making oral intake difficult. (**Figure 2A-D**) This patient also identify as men who have sex with men with multiple partners, HIV status was not known at the initial presentation. HIV screening was done with positive results.

Mpox is a re-emerging infectious disease that is considered a public health concern.[2] Mpox's main features is skin lesions that can vary in presentation. In patients in the high-risk group who develop new onset skin lesions, the clinician should keep mpox as a differential diagnosis.[1] Early case detection will minimize transmission risk and may warrant early treatment.

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The Impact on Working Conditions and Income Amongst Internists in Indonesia: Lesson Learned from the COVID-19 Pandemic

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ABSTRACT

Internists are at the forefront of providing care for COVID-19 patients. This situation adds more strain on already overburdened internists, particularly in Indonesia, where resources are scarce and unevenly distributed. The pandemic altered working conditions due to restrictions and regulatory changes. Multiple evidence exists for the effect of the COVID-19 pandemic on physicians' well-being, but less is known about its impact on their work dynamics and livelihoods. This study provides some lessons learned during the COVID-19 pandemic regarding the changes in working conditions and earnings experienced by Indonesian internists.

There were 3,115 and 1,772 participants in the first and second survey, respectively. After one year, the proportion of internists handling COVID-19 cases, including critical COVID-19 cases, increased; with fewer internists over 60 years old involved. Working hours, number of patients, and monthly earnings decreased for the majority of internists. The increased workload was experienced by most participants one year of the pandemic, predominantly reported by female internists.

The COVID-19 pandemic caused a considerable impact on working conditions and income amongst internists in Indonesia. These findings may provide information to institutions in formulating strategies and tools to improve the working conditions and livelihoods of internists in Indonesia amidst the pandemic and potential public health emergencies in the future.

Keywords: *COVID-19, working conditions, monthly earnings, internist, LMIC.*

INTRODUCTION

The COVID-19 pandemic starting in 2020 has caused a global crisis in which internists were heavily involved in providing care for COVID-19 patients. That situation added even more strain on already overburdened internists, particularly in low and middle-income countries (LMIC). This is notably true in Indonesia where resources are scarce and unevenly distributed. There were 4,584 and 4,665 Indonesian internists

working in June 2020 and February 2021, respectively. However, the concentration varied, and most internists practiced in Java (57.13%).[1,2]

As a result of the COVID-19 rapid spread, internists were faced with increasing clinical and nonclinical stressors. Working conditions and environment were altered due to pandemic restrictions and associated regulatory changes. Senior physicians tended to work from home during the pandemic and all physicians were advised to limit their number of patients and decrease their working hours.

Multiple evidence exists for the effect of the COVID-19 pandemic on the physical and mental well-being of physicians[3–5], but less is known about its impact on their work dynamics and livelihoods; especially in internists in LMICs. This study provides some lessons learned from the COVID-19 pandemic regarding the changes in working conditions and earnings experienced by Indonesian internists.

METHODS

Two nationwide cross-sectional surveys amongst Indonesian Society of Internal Medicine (*Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia, PAPDI*) members were conducted two times. The first survey was done 6 months after the start of the pandemic (June 2020) and the second survey was done 1 year after the start of the pandemic (February 2021). The inclusion criteria were Indonesian internists who were registered as Indonesian Society of Internal Medicine members. To participate, respondents were needed to be able to access the survey using a computer or smartphone. Participants who refused to participate in the study or did not fill out the online questionnaire completely were excluded from the analysis.

All of the data were collected via an online questionnaire in Indonesian using Google Forms, comprising 51 questions divided into 4 parts: demographic data, working conditions, and monthly earnings. Questions regarding changes in the second survey were compared to the first survey. During the data collection period, the questionnaire was distributed to the internists using email, PAPDI's official website, PAPDI's official social media accounts, and messaging applications.

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo Hospital. Consent was obtained from the participants using an informed consent form on the first page of the survey, declaring that the questionnaire was filled out voluntarily. Methods conducted in this study were by the Declaration of Helsinki. Data were analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL). Unless stated otherwise, continuous data were presented as mean or median, while categorical data were presented as frequency and percentage.

RESULTS

A total of 3,116 internists responded to the first survey, one of which was removed due to incomplete data. The analysis included 3,115 participants with a median age of 44 years (interquartile range [IQR]: 38–53). Of all respondents, 1,907 (61.3%) were male. Most respondents resided in Java (53.8%), followed by Sumatra, Central Indonesia, and Eastern Indonesia (25.8%, 11.7%, and 8.7%, respectively). In the second survey, a total of 1,773 internists responded, of which 1 was removed due to incomplete data. A total of 1,772 participants were included in the analysis with a mean age of 45.31 (SD = 10.05) years. Most of the respondents were male (82.4%), with a similar distribution regarding location. Study demographics can be seen in detail in **Table 1**.

Involvement in COVID-19 Management

In the first survey, 67.0% of participants worked in COVID-19 referral hospitals, 62.2% were appointed to the COVID-19 response team, and 67.4% were involved in handling COVID-19 patients, of which 42.6% also handled severe or critical COVID-19 cases (**Figure 1A**). However, only 50.2% were assigned as the physicians in charge. Additionally, 37.6% of internists experienced an increased workload in the first six months of the pandemic. This condition changed six months later in the second survey. The percentage of internists working in COVID-19 referral hospitals increased by 19.6%, and 12.9% more internists were appointed to the

Table 1. Respondent Characteristics.

Characteristics	6 months of the COVID-19 pandemic (n = 3,115)	1 year of the COVID-19 pandemic (n = 1,772)
	n (%)	n (%)
Sex		
Male	1,909 (61.3)	1,461 (82.4)
Female	1,206 (38.7)	311 (17.6)
Age group		
≤ 40	1,164 (37.4)	723 (40.8)
41–60	1,597 (51.3)	878 (49.5)
>60	354 (11.4)	171 (9.7)
Location		
Java	1,677 (53.8)	934 (52.7)
Sumatera	804 (25.8)	464 (26.2)
Central Indonesia	364 (11.7)	262 (14.8)
Eastern Indonesia	270 (8.7)	112 (6.3)

COVID-19 response team. The involvement of internists in COVID-19 cases also increased by as much as 19.2%, and 71.7% were assigned as physicians in charge. **Figure 2** displays the proportion of COVID-19 patients handled by internists compared to non-COVID-19 patients. Notably, the number of internists handling severe or critical COVID-19 cases almost doubled to 80.9%. Furthermore, the percentage of internists reporting an increased workload in the second survey increased by 15.6%.

Figure 1B demonstrates the involvement of COVID-19 management by age. Compared to other age groups, fewer internists over 60 years old worked in COVID-19 referral hospitals, were appointed as the hospital's COVID-19 response team, handled COVID-19 patients, and treated critical cases. Most internists working in COVID-19 referral hospitals were 40—60 years old (72.2%), but younger internists under 40 years old dominated the COVID-19 response team (86.0%) and handling of COVID-19 cases (95.0%), including being the physicians in charge (84.0%). In the second survey, the overall numbers increased in all age groups. Notably, the number of internists under 40 years old handling severe or critical COVID-19 cases doubled (from 46.7% to 91.0%). There were no discernible differences in the involvement of COVID-19 management between both sexes as seen in **Figure 1C**. In the second survey, there was a 30.7% increase in the proportion of female internists assigned as physicians in charge, compared to the 20.1% increase in male internists. In addition, compared to the male participants, more female physicians experienced an increased workload both in the first (43.0% vs 34.2%) and second (65.0% vs 50.7%) surveys.

Changes in Working Conditions

In the first 6 months, 59.2% of internists experienced a decrease of more than 50% in working hours and 57.5% reported a decrease of more than 50% in the number of patients compared to before the pandemic (**Figure 3A**). Reduction in working hours was more prevalent in internists over 60 years old (50.8% experienced less than a 50% decrease and 28.5% experienced more than a 50% decrease in working hours). Similarly, more internists over 60 years old reported a more than 50% decrease in the number of patients compared to other age groups as seen in **Figure 3B**. In the second survey, internists over 60 years old who experienced no change in working hours remained steady, albeit the majority still reported a decrease.

The number of consultations and night shift schedules remained steady for most internists (69.9% and 64.6% for the first and second surveys, respectively) as displayed in **Figure 4A**. Accounting for age, more internists over 60 years old experienced a decrease in the number of consultations and night shifts compared to other age groups in the first survey. Both sexes experienced similar changes in the first and second surveys.

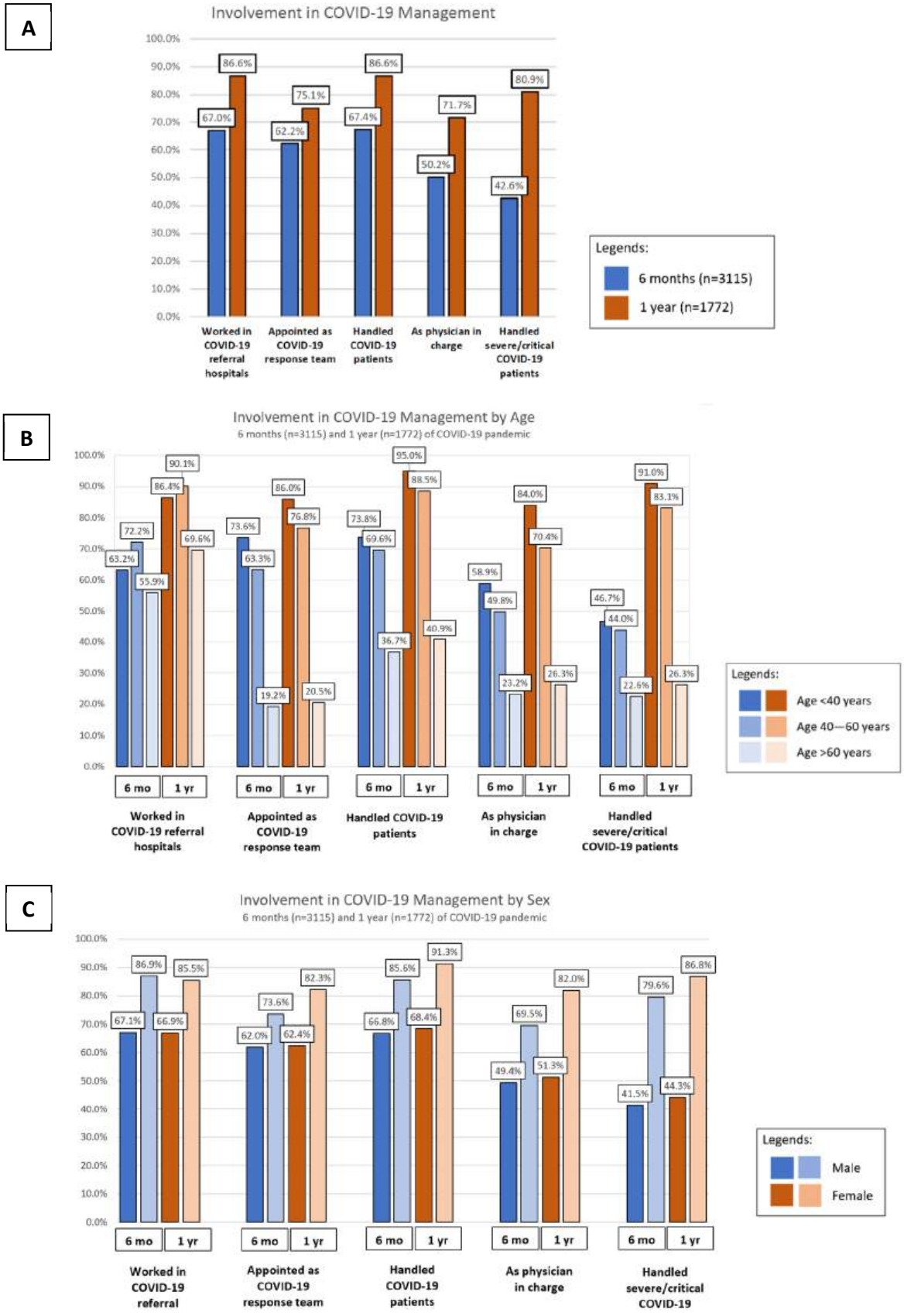

Figure 1. Involvement in COVID-19 management during 6 months and 1 year of the COVID-19 pandemic (A) and further categorizing by (B) age and (C) sex.

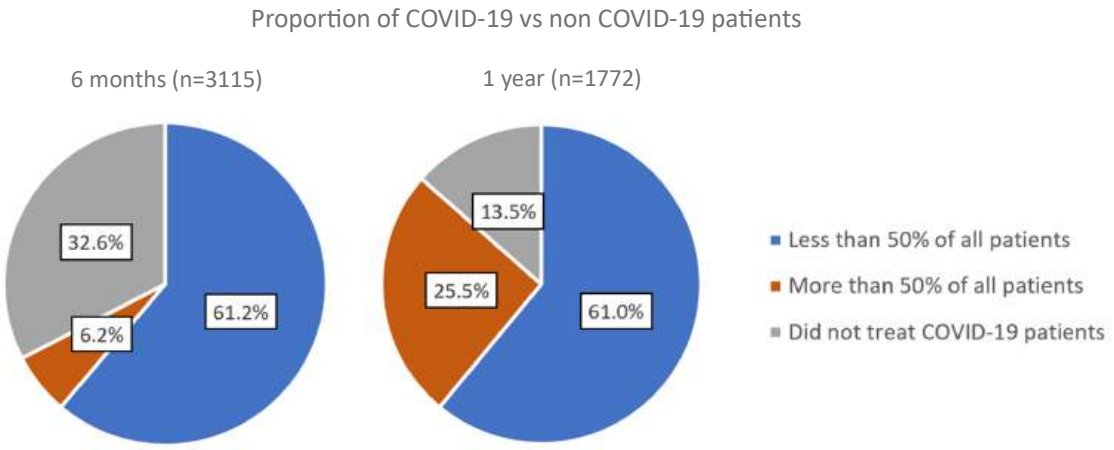

Figure 2. Proportion of COVID-19 vs non-COVID-19 patients in 6 months (n = 3115) and 1 year (n = 1772) of the pandemic.

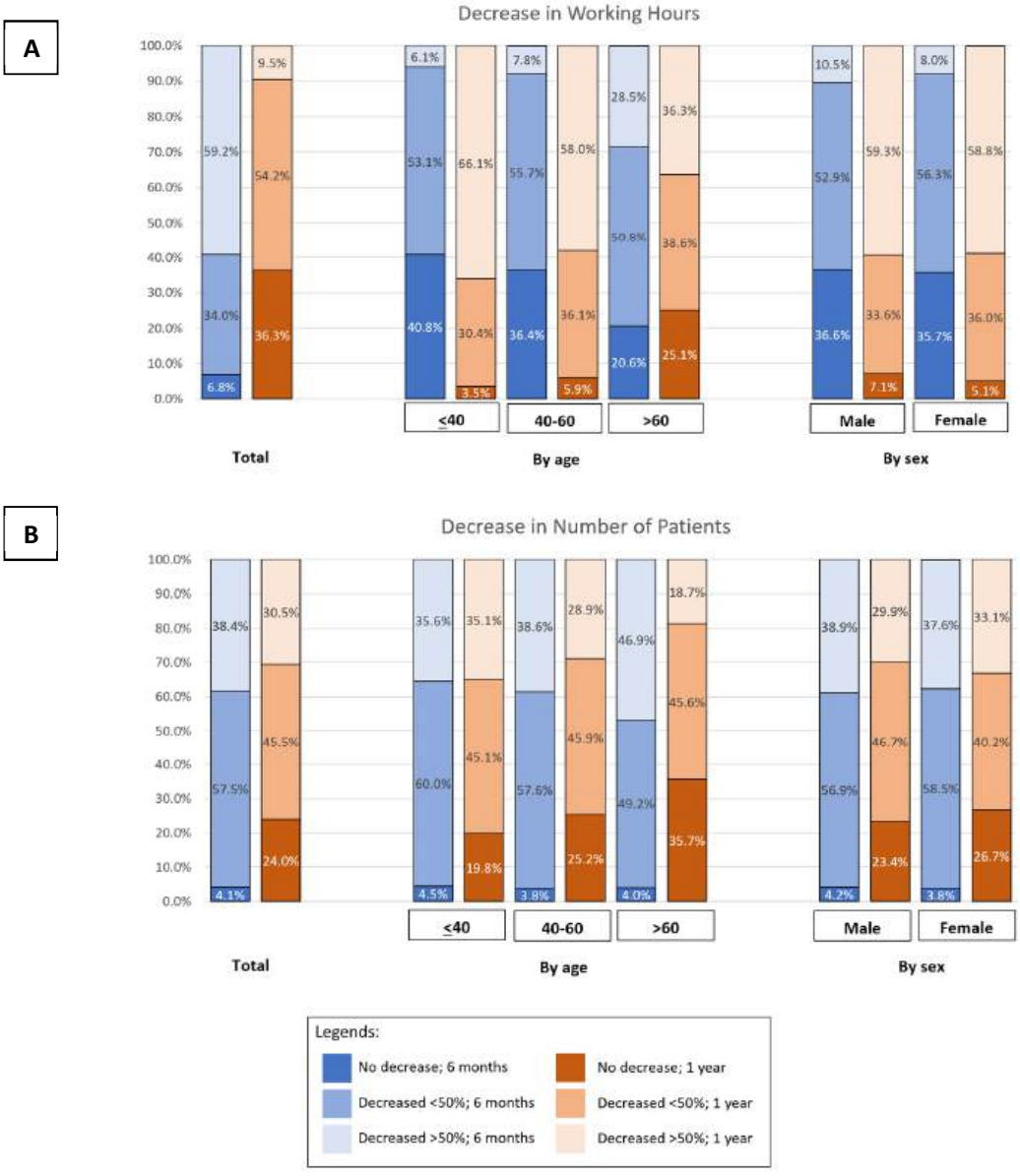

Figure 3. Decreases in (A) working hours dan (B) number of patients in 6 months and 1 year of the COVID-19 pandemic.

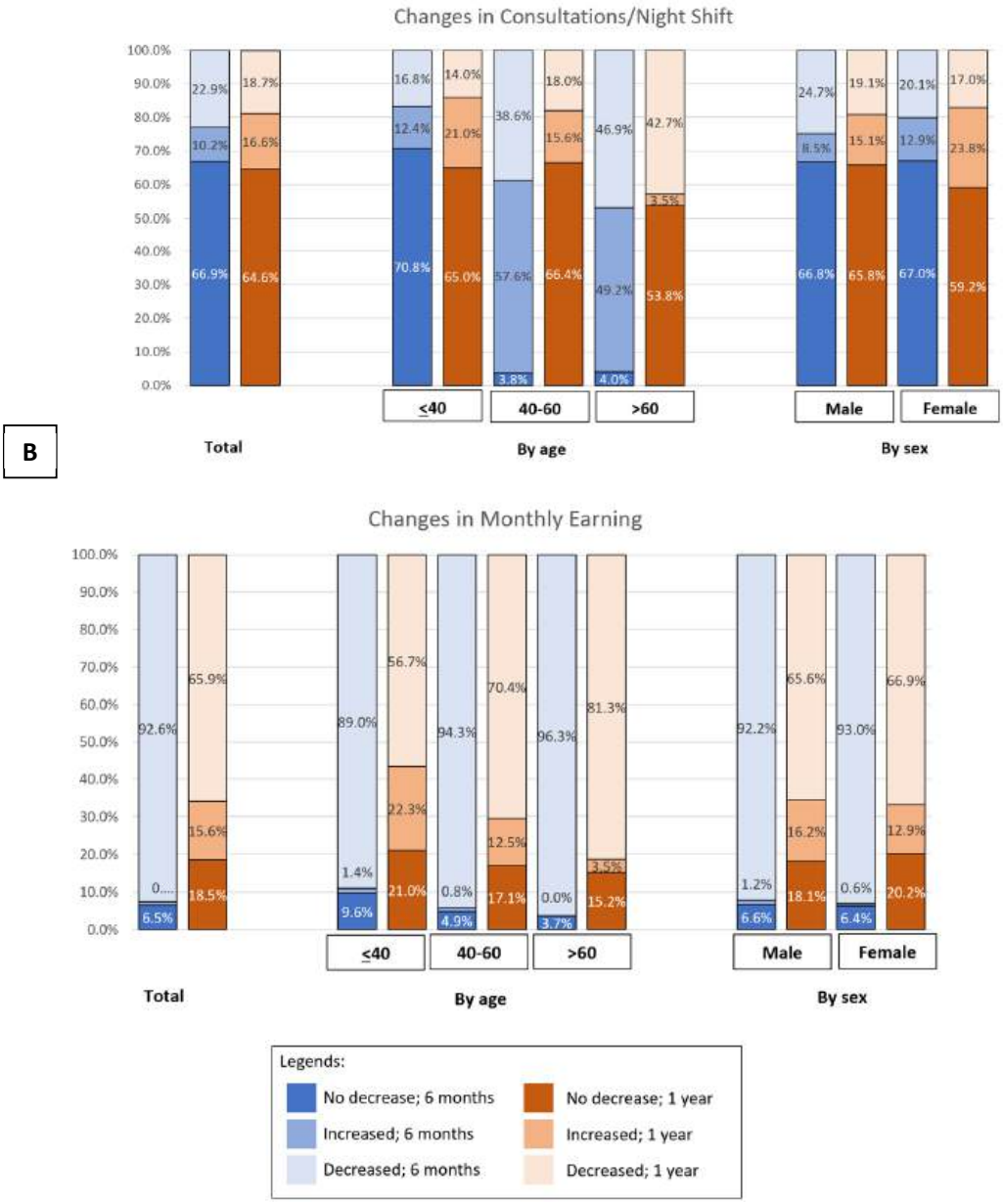

Figure 4. Changes in (A) number of consultations or night shifts and (B) monthly earnings in 6 months and 1 year of the COVID-19 pandemic.

A decrease in monthly earnings was experienced by nearly all of the respondents in the first survey (92.68%). More than half (65.9%) of participants saw a decrease in income six months later in the second survey, particularly in the 40—60 and over 60 age groups (Figure 4B). Among internists over 60 years old, there was a predominance of those who reported a reduced income at six months and one year of the COVID-19 pandemic (96.3% and 81.3%, respectively). The proportion of internists who experienced a decrease in monthly income was similar in both sexes.

DISCUSSION

During the first survey, confirmed COVID-19 cases reached 55,092 cases with a mortality rate of 2.85 (CFR 5.1%).[6] The number increased to 735,124 cases with a 21.944 mortality rate (CFR 3.0%) six months later in the second survey.[7] To overcome the increased number of patients, the Indonesian government appointed hundreds of COVID-19 referral hospitals. By October 12, 2020, there were 903 COVID-19 referral

hospitals in Indonesia, and each was given the liberty to form its own COVID-19 response team.[8] In this study, most of the internists worked in COVID-19 referral hospitals and were included in the COVID-19 response team. The majority also handled COVID-19 cases, including patients infected with severe or critical COVID-19. The involvement of internists in the management of COVID-19 was increased in the second survey, in line with the surge in COVID-19 cases.

Only half of internists (50.2%) who handled COVID-19 cases were assigned as the physicians in charge in the first survey, but the numbers rose to 71.7% six months later. This number was similar to a study done by Cheong et al, who reported that 80% of patients hospitalized for COVID-19 were mostly treated by internists, especially the infectious disease physicians.[9] Internists were heavily involved after one year of the pandemic, possibly due to a better understanding of COVID-19, its interplay with preexisting conditions, comorbidities, and complications that involve multiple organ systems.[10]

A smaller proportion of older doctors over 60 years old worked in referral hospitals, took part in COVID-19 response teams, and handled COVID-19 cases. This might be because older physicians over 60 or physicians with chronic conditions were urged not to practice directly with patients during the pandemic in Indonesia.[11] No notable discrepancy was noted between the proportion of male and female internists in this regard. This result contrasted with a study done by Soares et al., which reported that male physicians were more likely to handle COVID-19 patients.[12]

Our study showed that most internists in Indonesia reported a reduction in working hours during the pandemic. The regular working hours for the general population in Indonesia are 40 to 42 hours per week, but the numbers vary between physicians depending on the healthcare facility or unit. This decrease in working hours was also experienced by other medical practices worldwide.[13] A survey conducted in early May 2020 by the Texas Medical Association showed that 68% of doctors saw a reduced working hours during the pandemic.[14] Compared to January 2019, the average weekly hours worked by US physicians dropped significantly from 50.8 hours to 47.5 hours in May 2020.[15] de Oliviera et al. reported changes in the working hours of 1,182 physicians in Brazil during the COVID-19 pandemic. The study demonstrated that working hours were increased for physicians working in the public sector, while most of the private-only physicians saw a decrease.[16]

Nearly all participants in our study experienced a declining number of patients during the pandemic. This is in line with a study on general physicians in Germany which showed that the number of patient per week was significantly reduced by 49.0% during the COVID-19 lockdown.[17] During the initial two months of the COVID-19 pandemic, Baum et al. found that outpatient visits in the US Department of Veterans Affairs declined by 55.5%.[18] Byun et al. also reported a decrease of 10.2% in the number of outpatient internal medicine visits in South Korea from March to April 2020.[19] Although the number of patients decreased for most internists, half of our study's respondents had no changes in the number of consultations or night shift schedule.

The decline in working hours and number of patients during the pandemic may suggest the changes in health behavior, such as reduced social contacts and the tendency to watch and wait. External factors such as medical institutions' lockdowns, fear of hospital-acquired infection, and the stigma of confirmed COVID-19 infection may play a role in the decrease in healthcare utilization. Improved flexibility brought by COVID-19-driven policies can also contribute by allowing patients to receive medical services via telemedicine. Indeed, the COVID-19 pandemic urged many practitioners to incorporate teleconsultation into their practice. Unfortunately, we have no data about the condition after the pandemic in Indonesia. A survey evaluating the use of telemedicine in the post-pandemic era among French oncologists revealed some barriers encountered by the practitioners, including the lack of physical examination, technical difficulties (network, connection, sound), and

additional workload (if the teleconsultations are not part of their standard schedules). Thus, teleconsultation should be used as an adjunct to in-person visits and integrated into standard consultation schedules.[20]

Despite the reduced working hours and number of patients, 37.6% of internists experienced an increased workload in the first survey. This number surged by 15.6% after one year of the COVID-19 pandemic. Some reasons might affect these results. In our survey, the number of patients generally decreased for most internists, but the proportion of COVID-19 patients increased. The increased workload was mostly experienced by internists under 40, who mostly functioned as physicians in charge compared to those of other age groups. The escalating number of COVID-19-related-hospitalization imposed burdens on internists, especially when the disease's complexity was still novel and unpredictable in the first few months of the pandemic.[10] Furthermore, internists are not only responsible for handling COVID-19 cases and their complications but also various other internal medicine conditions. This may also be further aggravated by the morbidity and mortality of physicians due to COVID-19 infection. There is no official report on the COVID-19 infection rate amongst physicians in Indonesia, but a study by Soebandrio et al. reported that from March to May 2020, 46 out of 1,201 specimens obtained from healthcare workers in Jakarta tested positive for COVID-19.[3] Additionally, according to the Indonesian Medical Association (IMA), the number of doctors who died in Indonesia was amongst the highest in the world.[21] Until March 2023, a total of 2,172 doctors died of COVID-19.[22] Moreover, increasing number of research projects and online meetings outside of working hours may also contribute to the increased workload amongst internists during the COVID-19 pandemic.

More female internists in this study perceived an increased workload both at six months and one year after the pandemic. An Italian survey of physicians and other healthcare professionals found that women were more likely to report an increased workload during the pandemic.[23] Female physicians working as frontline providers have been demonstrated to have a greater complexity of work-life balance, evidenced by spending 8.5 more hours per week on child-rearing and domestic tasks compared to their male counterparts.[24] Furthermore, the COVID-19 pandemic exacerbated these obstacles by forcing school closures and childcare restrictions during lockdown.[25,26] Morgan et al. reported that during crises (pandemics, epidemics, and natural disasters), female healthcare workers were more likely to experience an increased workloads and caregiving responsibilities at home.[27] During the pandemic, women have been compelled to reduce their working hours four to five times more than men due to childcare and domestic work.[28]

A decrease in monthly income was experienced by nearly all respondents. The COVID-19 pandemic has had a detrimental impact on medical practices worldwide, especially regarding decreased revenue. The American Medical Association (AMA) survey in July and August 2020 reported that out of 3,500 physicians, 81% experienced a drop in income compared to the pre-pandemic era with an average of 32% decrease.[29] De Oliveira et al. also reported that the earnings of physicians in the public sector in Brazil remained stable, while 52.2% of private-only physicians reported a decrease in their monthly earnings.[16] This negative economic impact seemed to have a greater effect on already vulnerable groups, including senior citizens.[30] This is reflected in the findings of our study, in which 96.3% and 81.3% of internists over 60 reported a reduced monthly earnings six months and one year after the COVID-19 pandemic, respectively.

There are several strengths and limitations in this study. To the best of our knowledge, this was the first study describing the working conditions of Indonesian internists during the COVID-19 pandemic. The nationwide survey covered a broad geographical scope with a large sample size, which represented all provinces in Indonesia. However, this was a self-reported survey, therefore the possibility of underreporting, recall bias, and social desirability bias was likely. Because the survey was held online, only internists who had access to computers or smartphones and internet

access could take part. Due to the anonymous nature of the survey, the association between the six-month and one-year results cannot be deduced. Moreover, the cause-and-effect relationship cannot be determined due to the cross-sectional study design.

CONCLUSION

The COVID-19 pandemic has had a considerable impact on working conditions and earnings amongst internists in Indonesia. Most of the internists in this study were included in the COVID-19 response team and handled COVID-19 cases, including critically ill patients. Most participants also reported reduced working hours, number of patients, and monthly payments in six months and one year of the pandemic, especially female internists and internists under 40 years old. These findings may provide information to institutions in formulating strategies and tools to improve the working conditions and livelihoods of internists in Indonesia amidst the current pandemic and potential public health emergencies in the future.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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Consensus Guidelines for Influenza Vaccination in Patients with Diabetes

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ABSTRACT

Influenza is a prevalent health issue encountered in daily practice. Patients with diabetes mellitus face a higher risk of infections, including influenza, owing to the compromised immune system associated with diabetes. This susceptibility arises from the potential of diabetes mellitus to weaken the immune system. Moreover, elevated blood glucose levels can create a conducive environment for the growth of bacteria and viruses. This consensus is formulated by a multidisciplinary team to serve as practical guidance for the administration of influenza vaccinations to patients with diabetes mellitus in daily practice.

Keywords: *influenza, diabetes mellitus, vaccination*

INTRODUCTION

Influenza and Influenza-like Illness (ILI) are respiratory infections that are clinically challenging to distinguish because routine diagnosis is rarely performed. Influenza occurs throughout the year in Indonesia with spikes in certain months and every year, various strains of influenza viruses A (A/H1N1, A/H3N2) and B (B/Victoria and B/Yamagata) circulate simultaneously.[1] In a 2019 study related to the occurrence of ILI and Severe Acute Respiratory Infection (SARI) in East Jakarta, Indonesia, the contribution of Influenza showed significant figures (31% in ILI, 15% in SARI).[2] Research in 2011 estimated that there are approximately a total of 4 million flu cases in Indonesia every year, resulting in nearly 200,000 hospitalizations related to the flu.[3]

Diabetes mellitus (DM), both type 1 and type 2, remains a significant health issue in Indonesia. According to the 2018 Basic Health Research (Riskesdas) report, the prevalence of diabetes mellitus in Indonesia increased from 6.9% to 8.5%.[4] In 2021, the International Diabetes Federation (IDF) reported approximately 19.46 million adults with DM, ranking Indonesia as the 5th highest country in the world regarding the number of individuals affected by diabetes.[5] Diabetes mellitus (DM) can weaken the immune system, making it more challenging for the body to fend off infections. Moreover, elevated blood sugar levels create a favorable environment for the growth of bacteria and viruses, thus increasing the risk of infection. DM can also harm blood vessels and nerves, leading to impaired circulation and delayed healing times. Consequently, individuals with DM are at a higher risk of contracting infections, including influenza.[6]

The burden of influenza in the diabetic population, compared to influenza patients without diabetes, increases significantly.[7] It can be up to 6 times greater for the risk of hospitalization, 4 times higher for the risk of intensive care unit (ICU) admission[8], and 6 times higher for the risk of death.[9] Patients infected with influenza also exhibit significantly higher average Diabetes Complications Severity Index (DCSI) scores compared to the non-influenza group. This leads to an increase in overall healthcare costs for diabetic patients with influenza.[10] According to various reports, managing influenza can incur very high costs, including both direct costs related to outpatient and inpatient care and indirect costs associated with transportation, disease management, and mortality.

This consensus is formulated as a guideline for doctors to administer influenza vaccination to patients with diabetes mellitus (DM). Currently, influenza vaccination for patients with DM is already recommended in the Adult Immunization Schedule as per the Immunization Task Force of the Indonesian Society of Internal Medicine 2023, as well as in the Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus in Adults in Indonesia published by the Indonesian Society of Endocrinology in 2021.

INFLUENZA VIRUS

Virus Types

There are four types of influenza viruses: influenza types A, B, C, and D. Influenza A and B are responsible for seasonal epidemics in populations (commonly referred to as seasonal flu) nearly every winter in the United States. Influenza A is known for causing flu pandemics. Influenza C typically causes mild symptoms and does not result in epidemics in humans. Influenza C primarily infects livestock, with transmission to other animals, but it is not known to transmit to humans. Influenza A viruses are further divided into subtypes based on two proteins on the virus's surface, namely hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (H1 to H18 and N1 to N11). There are over 130 known combinations of influenza A subtypes found in nature, primarily among wild birds. These combinations of influenza subtypes have the potential to re-emerge due to the exchange of genetic segments from the virus genes (reassortment). Reassortment can occur when two types of influenza viruses infect a host simultaneously and exchange genetic information. Subtypes of influenza A that regularly circulate among humans include H1N1 and H3N2. Influenza B is categorized into Victoria and Yamagata lineages. These subtypes can further break down into smaller genetic segments called "clades" and "subclades." Influenza types A and B play a role in seasonal flu every year. Influenza A (H3N2 or H1N1) undergoes genetic changes seasonally and can lead to less effective immune responses in humans. Influenza B can experience similar changes, but at a slower rate compared to influenza A. Influenza virus, particles have a diameter of 80-120 nanometers and have a spherical shape. The composition of the virus particle includes a capsule containing two types of glycoproteins that envelop a central core. This core contains RNA genomes and other viral proteins that encapsulate the RNA.[34,35]

Symptoms and Signs

Seasonal influenza infections are characterized by sudden onset of fever, dry

cough, headache, muscle and joint pain, severe malaise, sore throat, and runny nose. Cough can be severe and persist for 2 weeks or more. Influenza virus transmission can occur easily, especially in crowded places such as schools or nursing homes, and it is transmitted through respiratory droplets. The virus incubation period is approximately 2 days, varying from 1 to 4 days. Generally, infected individuals recover from fever and other symptoms within 1 week without requiring special attention. However, influenza can cause severe illness and death in high-risk groups. These high-risk groups include pregnant women, children under 59 months of age, elderly population, individuals with chronic diseases such as chronic heart disease, chronic kidney disease, metabolic disorders (diabetes mellitus, liver disorders, or hematological conditions), individuals with immunocompromised conditions (e.g., HIV, undergoing chemotherapy or taking steroids, and malignancies), healthcare workers that are at high risk of contracting the influenza virus due to their high exposure to patients and are also susceptible to transmitting to high-risk individuals.[36,37]

Epidemiology

Worldwide, influenza is estimated to cause severe illness in 3-5 million cases annually and result in 290,000 to 650,000 deaths each year. A surveillance study of influenza in Indonesia from 2003 to 2007 reported 21,030 cases with clinical manifestations resembling influenza. Out of this total, 4,236 cases (20.1%) were confirmed to be infected with influenza viruses, with a similar proportion among outpatient and inpatient cases. The age group most affected by influenza was school-aged children. This study also found that 64.9% of all identified influenza cases were caused by influenza A viruses (with subtypes H3N2 accounting for 64.6%, H1N1 for 34.9%, and H5N1 for 0.4%), while the remaining 35.1% were caused by influenza B viruses. Seasonal activity of influenza A viruses was observed, with peak incidence occurring in December and January during the rainy season, particularly in western and central Indonesia. In eastern Indonesia, both influenza A and B viruses were found to be active.[37,38]

Diagnosis

In general, influenza infection is clinically diagnosed. However, infections from other respiratory viruses, such as rhinovirus, respiratory syncytial virus (RSV), parainfluenza, and adenovirus, can also cause symptoms similar to influenza (influenza-like illness/ILI). This makes it challenging to differentiate clinical symptoms caused by influenza infection from other pathogens. Obtaining a good respiratory sample for laboratory diagnostic testing is necessary to establish a definitive diagnosis. Laboratory confirmation from throat, nasal, and nasopharyngeal samples is commonly performed using examinations such as antigen tests or PCR.[35,37]

Treatment and Prevention

Patients who are not at high risk can be managed with symptomatic treatment. Patients with severe symptoms can be treated with antiviral medications such as neuraminidase inhibitors (e.g., oseltamivir), which are recommended to be administered as soon as possible within 48 hours of symptom onset and continued for at least 5 days, depending on clinical improvement. Corticosteroids are not commonly administered unless in specific cases such as the presence of asthma. The use of corticosteroids also has the potential to cause immunosuppression and prolong viral clearance. The most effective prevention method is vaccination. Influenza vaccination is safe and highly effective. The World Health Organization (WHO) recommends annual influenza vaccination for the following groups: pregnant women, children aged 6 months to 5 years, the elderly population, individuals with chronic diseases, and healthcare workers.[34,37]

INFLUENZA INFECTION AND DIABETES MELLITUS

Patients with diabetes mellitus (DM) have weakened immune responses, impairments in chemotaxis, phagocytosis, and antigen presentation in response to infections. This leads to disruptions in the function and proliferation of T cells, ultimately exacerbating the symptoms of infectious diseases.[39] Impairments in innate immunity in DM patients are associated with the complement system, cytokines, and

hyperglycemia. A study conducted on 86 patients found that 26% of them had low complement levels (C4), resulting in neutrophil dysfunction and inadequate cytokine responses. Lower secretion of interleukin-1 (IL-1) and interleukin-6 (IL-6) by mononuclear cells and monocytes was also observed in DM patients when stimulated by bacterial components such as lipopolysaccharides (LPS) activated through phagocytosis.[40] In conditions of hyperglycemia, reduced neutrophil degranulation, complement activation, and impaired phagocytosis have been reported. This results in more severe symptoms of respiratory infections, including influenza.[41] A study in Canada reported that DM patients had a threefold higher risk of experiencing severe symptoms and hospitalization during the H1N1 pandemic in 2009. ICU admissions were four times higher in DM patients compared to non-DM patients.[8] A study in Germany by Wilking et al. reported that deaths due to the influenza strain circulating in 2009 were twice as high in DM patients compared to non-DM patients. Influenza infection can also worsen blood glucose control and increase DM complications.[39] Apart from causing more severe complications, influenza infections are known to trigger the onset of DM. A study by Nenna et al. in Rome found an increased incidence of newly diagnosed type 1 DM following the H1N1 pandemic (October 2009 to January 2010) compared to the years 2004-2005. Additionally, an increase in newly diagnosed type 1 DM was reported in the 1970s following an influenza epidemic.[42]

Respiratory tract infections caused by influenza viruses are transmitted through droplets and aerosols, making them highly contagious and capable of causing serious complications in individuals with weakened immune systems.[7] The disease burden of influenza in the diabetic population, compared to influenza patients without diabetes, increases significantly, resulting in up to a six-fold greater risk of hospitalization, a four-fold increase in the risk of intensive care unit (ICU) admission[8], and a six-fold increase in the risk of death.[9]

Furthermore, a retrospective study indicates that the rate of diabetes complications increases following exposure to the influenza virus. Patients who have been infected with influenza tend to have significantly higher average Diabetes Complications Severity Index (DCSI) scores compared to those in the non-influenza group.[10] The same study also highlights a higher utilization of healthcare services, including outpatient visits, emergency department visits, and hospitalizations, resulting in an overall surge in healthcare costs for individuals with diabetes who also contract influenza.

Based on the research by Kosen et al. in 2017, the impact caused by lower respiratory tract infections attributed to influenza in Indonesia is highly significant. The disease burden is estimated to reach 3,358,418 cases of influenza-related lower respiratory tract infections, including 40,435 hospitalizations and 4,097 deaths. The estimated cost incurred is approximately US$ 866.7 million. This total includes indirect costs of US$ 847.5 million associated with productivity loss and direct costs of US$ 19.2 million related to treatment expenses.[3] Meanwhile, according to the study by Akin et al. in Turkey, increasing influenza vaccination coverage to 20% in the adult population with type 2 diabetes mellitus (DM) is predicted to prevent 19,777 cases of influenza, 2,376 hospitalizations, and 236 deaths. The cost savings from influenza treatment are estimated to be 8.3 million Turkish lira, while the cost of vaccination amounts to approximately 8.4 million Turkish lira.[21] Furthermore, research conducted by Wang et al. in Taiwan demonstrates that influenza vaccination provides considerable cost benefits for patients with DM. An estimated 1,283 USD can be saved per hospitalization event in DM patients who receive the influenza vaccine compared to those who do not.[20] Influenza vaccination is a primary preventive measure in reducing the incidence of hospitalizations and deaths due to influenza virus.[11] Influenza vaccination is indicated for adults and is highly recommended for the elderly, pregnant women, children under 5 years of age, travelers, people with chronic diseases, and healthcare workers.[12]

INFLUENZA VACCINE TYPES

The World Health Organization (WHO) issues recommendations every February and

September each year to suggest the strains of the influenza virus be included in vaccines for the Northern and Southern hemispheres. In Indonesia, influenza vaccination can be administered throughout the year using the available influenza vaccines at that time. For travelers, vaccines are tailored to the destination region. Influenza vaccines are categorized into three types: live-attenuated influenza vaccine (LAIV), inactivated influenza vaccine (IIV), and recombinant influenza vaccine (RIV), with their usage tailored to different age groups.[13] In Indonesia, the available influenza vaccine is the Inactivated Influenza Vaccine (IIV). Based on the contained strain types, there are two main types of influenza vaccines. First, Trivalent Inactivated Influenza Vaccine (IIV3) provides protection against two influenza A strains (A/H1N1 and A/H3N2) and one influenza B strain (B/Victoria or B/Yamagata). Second, Quadrivalent Inactivated Influenza Vaccine (IIV4) offers protection against two influenza A strains (A/H1N1 and A/H3N2) and two influenza B strains (B/Victoria and B/Yamagata). Quadrivalent influenza vaccines provide additional protection compared to trivalent vaccines because they cover both influenza B strains (B/Victoria and B/Yamagata) that co-circulate in the wild.[14]

BENEFITS OF INFLUENZA VACCINATION IN THE DIABETES POPULATION

Patients with diabetes are considered a high-risk population and are more likely to experience complications, hospitalizations, and mortality due to influenza infections. Therefore, influenza vaccination for diabetes patients is recommended as the standard of care for managing all patients with type 1 and 2 diabetes.[15] Furthermore, diabetes patients with comorbid conditions are strongly advised to receive influenza vaccination. The comorbidities include chronic respiratory system disorders, chronic kidney disease, cardiovascular disorders (heart failure, coronary heart disease, acute coronary syndrome, hypertension, arrhythmia, heart valve disorders, congenital defects), immunocompromised conditions (HIV/AIDS, cancer, etc), cancer, anemia/hemoglobinopathies, morbid obesity and elderly individuals.[12]

The immune response of diabetes patients (seroprotection and seroconversion) after influenza vaccination is quite comparable to that of healthy adults. One month after vaccination, the seroconversion rate reaches 58.0%, and seroprotection reaches 99.0%. These review findings indicate that influenza vaccination protects them from severe infections and complications.[16]

Meta-analyses have shown that influenza vaccination in adult diabetes patients (aged 18-64 years) can reduce mortality rates and the incidence of hospitalization due to pneumonia.[17] Other studies have assessed that influenza vaccination in adult diabetes patients can significantly reduce the number of influenza cases and hospitalizations related to influenza events.[18] The benefits of influenza vaccination in elderly diabetes patients (aged 65 and above) also significantly reduce the incidence of influenza-like illness, hospitalization due to pneumonia or other reasons, and a decrease in mortality due to respiratory tract infections or any other cause.[17] A study conducted in the UK with 124,503 diabetic patients between 2003-2010 showed that influenza vaccination was associated with lower rates of hospitalization and mortality in vaccinated patients compared to those who did not receive vaccination. This study found a significant reduction in cardiovascular events, including acute myocardial infarction (19%), stroke (30%), heart failure (22%), and pneumonia (15%).[43] Another study by Wang et al. in elderly diabetic patients showed a reduction in hospitalization rates of up to 11% in patients who received influenza vaccination compared to those who did not receive vaccination.[44]

For diabetes patients with cardiovascular disease, influenza vaccination has been linked to a reduction in overall mortality risk, cardiovascular disease-related mortality risk, and the incidence of cardiovascular events.[19] Data from various countries also show that increasing influenza vaccination coverage in the diabetes population and reducing the number of cases, hospitalizations, and deaths can result in significant cost savings.[20,21]

INFLUENZA VACCINE ADMINISTRATION

In Indonesia, influenza vaccination can be administered throughout the year, using the available influenza vaccines at the time.[12] Annual influenza vaccination for type 1 and type 2 diabetes patients can begin at the age of 6 months and should be administered every year.[22] The American Diabetes Association (ADA) recommends the use of inactivated and recombinant influenza vaccines for diabetes patients and advises against the use of live attenuated vaccines (LAIV).[23] The influenza vaccines available in Indonesia are of the inactivated type and are administered intramuscularly (IM).

Influenza vaccination is needed annually because the influenza virus continues to mutate (antigenic drift), affecting various strains.[24] Therefore, influenza vaccines are updated yearly to protect against the viruses that will circulate in the upcoming season. Receiving an influenza vaccination more than one year after the previous vaccination is still beneficial, but the immune response from the previous vaccination will decrease over time.[25] Hence, if the virus strains remain unchanged, annual influenza vaccination is still necessary to maximize protection. In certain situations where the strains in the vaccine differ from the circulating strains in a specific region, revaccination can be administered before one year to enhance protection.[26] The CDC recommends that travelers going abroad should receive influenza vaccination at least 2 weeks before their trip.[27]

In general, there are no absolute contraindications to influenza vaccination, except for a history of severe hypersensitivity reactions to previous influenza vaccines. In specific situations, vaccination should be postponed if there are severe acute conditions.[13] Severe acute conditions in patients with diabetes include hypoglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic state. As long as these conditions are not present, vaccination is still recommended even if blood sugar levels are not well controlled. Influenza vaccination can be administered simultaneously with other vaccines. If the next influenza vaccination is given less than 1 year after the previous vaccination, it is generally safe and does not have significant cross-reactivity.[12]

Influenza vaccination should also be considered in diabetic patients as part of hospital care after a myocardial infarction episode. Influenza vaccination can be administered within 72 hours after a myocardial infarction episode. Besides diabetic patients, it is important for healthcare workers handling these patients to receive influenza vaccination because they are at higher risk of being exposed to the influenza virus, which could pose a risk of spreading it to other vulnerable patients.[29] In addition to healthcare workers, vaccination is also recommended for individuals living near people with diabetes, including family members of patients and caregivers.[30]

SAFETY PROFILE AND CONSIDERATIONS IN INFLUENZA VACCINATION

In addition to being effective, influenza vaccination is also safe and well-tolerated by adult and elderly diabetic patients.[16] Generally, the side effects that may occur are mild and include mild local reactions like pain at the injection site, swelling, or redness. Systemic side effects are also typically mild and may include myalgia and low-grade fever. If these side effects occur, they can usually be managed with the administration of paracetamol.[12] One study noted that there is a possibility of elevated blood sugar levels up to 24 hours after vaccination, but this is temporary and returns to the patient's previous blood sugar range one day after vaccination.[31] This reaffirms that the benefits of influenza vaccination outweigh the risks and addresses concerns among diabetic patients which can lead to decreased vaccination rates. However, diabetic patients with the following conditions should not receive influenza vaccination. First, individuals with a life-threatening allergy to any component of the influenza vaccine (whether it's egg protein or other components) should not receive the vaccine. Second, individuals who have experienced a severe allergic reaction to one dose of the influenza vaccine should not receive that specific vaccine again and may be unable to receive other influenza vaccines.[32]

Individuals who use immunosuppressants are generally safe to receive inactivated vaccines,

including influenza. However, their immune response to the vaccine may be reduced.[33] Diabetic patients with a history of non-severe egg allergy can receive licensed and recommended influenza vaccines, such as Inactivated Influenza Vaccine (IIV) and Recombinant Influenza Vaccine (RIV). The choice of vaccine should be administered under strict medical supervision. Vaccine administration should be monitored by healthcare providers capable of recognizing and managing severe allergic reactions.[34]

RECOMMENDATION

Influenza remains a disease with a significant burden in terms of both direct and indirect costs. Influenza infection in populations with diabetes mellitus (DM) poses a higher risk of morbidity and mortality.

Prevention is crucial, and one proven preventive measure is influenza vaccination. Influenza vaccination has been shown to prevent or reduce the severity of symptoms in DM patients if they become infected with influenza.

Influenza vaccination has a good safety profile when administered to individuals with comorbidities, particularly in populations with DM.

Recommended influenza vaccines include inactivated and recombinant types and should be administered annually.

CONCLUSION

This consensus provides a comprehensive guideline for healthcare practitioners to navigate the complexities of influenza management in patients with diabetes mellitus. The collaborative effort of the multidisciplinary team underscores the importance of a unified approach in addressing the heightened risks diabetes patients face during influenza. The integration of these recommendations into daily practice holds the potential to significantly reduce the overall healthcare burden associated with influenza in this vulnerable population.

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DECLARATION OF COMPETING INTEREST

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