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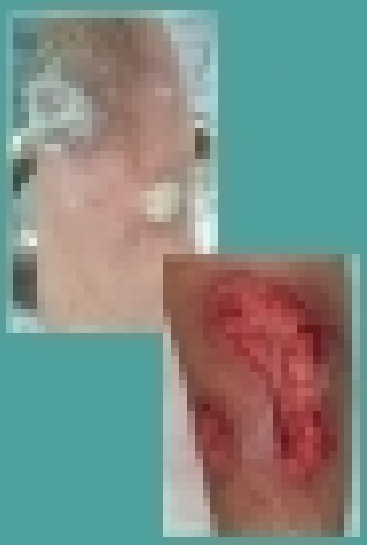

IJIM

Pulmonary Fibrosis Caused by Severe COVID-19 Infection: Discharge May Not Be The End of Treatment

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Since December 2019, COVID-19 caused by SARS-CoV-2 infection has been spread rapidly in the world. Beside acute respiratory distress syndrome found in acute phase of infection, there is also pulmonary fibrosis as a chronic complication due to COVID-19. With the global pandemic of COVID-19, more and more autopsy and puncture histopathological results have been published.[1] Liu et al.[2] reported the world's first case of gross anatomy of COVID-19 in elderly male, suggesting that most of the left lung showed gray-white patchy changes. There was also severe congestion of the right lung, showing dark red patchy. In the marginal area of lung, a large amount of gray-white mucus overflows and fibrotic cords can be seen after incision. Subsequently, Yao et al. reported three cases of puncture pathology. The pathological description was that the alveolar structure was destroyed in varying degrees and a small amount of serous and fibrin exudate were found in the alveolar cavity. The exudative cells are mainly monocytes and macrophages, with a few multinucleated giant cells, lymphocytes, eosinophils and neutrophils. The lymphocytes were mainly CD4 positive T cells. Type II alveolar epithelial cells proliferated significantly and some of these cells exfoliated to the alveolar cavity. There were also focal pulmonary hemorrhage, partial alveolar exudation and pulmonary interstitial fibrosis. Different degree of pulmonary fibrosis was found in pathological examination from all cases.[3]

Several studies have also found that cytokines (mainly transforming growth factor-β [TGF-β], IL-6 and TNF-α) involved in pulmonary fibrosis are increased, which indirectly suggest pulmonary fibrosis as a crucial component in the development of the disease. Up to 15% of COVID-19 patients developed acute respiratory distress syndrome (ARDS), and ARDS itself is one of the most important risk factors for developing of pulmonary fibrosis.[4] The factors mediating for profibrotic response to SARS-CoV-2 virus are not fully known, but from some studies suggest that age, severity of illness, use of mechanical ventilation, smoking and chronic alcoholism may contribute. Furthermore, the mechanisms by which SARS-CoV-2 infection may cause pulmonary fibrosis are also not fully understood. Although ARDS seems to be the main predictor of pulmonary fibrosis in COVID-19, several studies showed that COVID induced ARDS is different from the classical ARDS. Lung CT scan finding in many cases of are also not suggestive for classical ARDS. Therefore, mechanism of pulmonary fibrosis in COVID-19 is different from that of idiopathic pulmonary fibrosis (IPF), especially with pathological findings pointing to alveolar epithelial cells being the site of injury and not the endothelial cells. Most of study suggest that cytokine (especially TGF-β), fibroblast, angiotensin converting enzyme-2, ventilator induced-lung injury (VILI) and oxygen toxicity have an important role for developing of pulmonary fibrosis in COVID-19.[5,6]

The diagnosis of pulmonary fibrosis can be made based on clinical symptoms, radiologic information and history of severe ARDS due to COVID-19. Clinical symptoms of pulmonary fibrosis consisting of dry cough, fatique and dyspnea.[7] Lung CT scan finding from pulmonary fibrosis consisting of parenchymal bands, architectural distorsion and traction bronchiectasis.[8]

Until now there is no specific therapy to handle post-inflammatory pulmonary fibrosis due to COVID-19 infection. Several studies are ongoing to determine an effective treatment for this chronic complication. While ARDS appears to be the main cause of pulmonary fibrosis in COVID-19, the pathogenesis of ARDS caused by SARS-CoV-2 is different from the typical ARDS. Some therapies may be considered for reducing the fibrosis process in lung after COVI-19 infection namely pirfenidone, nintedanib and mesenchymal stem cells.[9-17] Many patients are still recovering spontaneously in the first six weeks after acute COVID-19 infection and do not generally require fast-track entry into a pulmonary rehabilitation programme. However, those who have significantly persistent respiratory illness may need to be supported by pulmonary rehabilitation. Multidisciplinary intervention based on personalized evaluation and treatment which includes exercise training, education and behavioral modification can be given to improve the physical and psychological condition of patients with post-COVID pulmonary fibrosis.[18]

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Validation of the Indonesian Version of the Asian Diabetes Quality of Life Questionnaire

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ABSTRAK

Latar belakang: *kualitas hidup telah me njadi salah satu parameter keberhasilan terapi, antara lain pada penderita diabetes melitus tipe 2, dan untuk menilai kualitas hidup diperlukan instrumen yang sesuai dengan latar belakang sosio-budaya populasi yang dinilai. Tujuan dari penelitian ini adalah untuk mengadaptasi kuesioner Asian Diabetes Quality of Life agar dapat digunakan di Indonesia dengan valid dan reliabel.* ***Metode:*** *kuesioner Asian Diabetes Quality of Life diterjemahkan dan diadaptasi ke dalam Bahasa Indonesia oleh tim ahli lalu dilakukan uji validitas dan reliabilitas pada pasien diabetes melitus tipe 2 di RSUP Dr. Hasan Sadikin Bandung. Validitas konstruk dianalisis dengan uji korelasi antara skor skala Likert setiap pertanyaan dengan skor total. Reliabilitas dianalisis dengan test-retest dan konsistensi internal menggunakan Cronbach's alpha.* ***Hasil:*** *uji validitas menunjukkan korelasi bermakna (p-value ≤ 0,05) antara skor setiap pertanyaan dengan skor total pada semua domain dengan rentang korelasi sedang sampai sangat kuat (r: 0,496-0,956). Uji reliabilitas test-retest menunjukkan tidak ada perbedaan bermakna antara hasil tes I dan II (p-value > 0,05) dengan korelasi sangat kuat (r: 0,830-0,975) serta konsistensi internal menghasilkan Cronbach's alpha ≥ 0,70 untuk seluruh domain.* ***Kesimpulan:*** *kuesioner Asian DQOL versi bahasa Indonesia memiliki validitas dan reliabilitas yang baik dalam menilai kualitas hidup pasien diabetes melitus tipe 2.*

Kata kunci: *kuesioner, validitas, reliabilitas, kualitas hidup, diabetes mellitus.*

ABSTRACT

Background: *quality of life has been identified as the goal of therapy especially in patient with chronic disease such as type 2 diabetes mellitus. Quality of life measurement requires an instrument that was specifically developed in accordance with socio-cultural background of the measured population. The aim of this study was to adapt Asian Diabetes Quality of Life Questionnaire so it can be used in Indonesia as valid and reliable tool.* ***Methods:*** *Asian Diabetes Quality of Life Questionnaire was translated and adapted by group of experts, then validity and reliability tests were conducted on type 2 diabetes mellitus patients at Dr. Hasan Sadikin General Hospital, Bandung. Construct validity was analyzed using correlation test between score of each item and total score. Reliability was measured using test-retest method and internal consistency represented in Cronbach's alpha score.* ***Results:*** *validity test showed significant correlation (p-value ≤0.05) between score of each item and total score across all domains with moderate to very strong correlation (r: 0.496-0.956). Reliability test using test-retest method showed no significant difference between Test I and II results (p-value >0.05) with very strong correlation (r: 0.830-0.975) and internal consistency yielded Cronbach's alpha scores of ≥ 0.07 for all domains.* ***Conclusion:*** *Indonesian version of Asian DQOL is a valid and reliable tool to measure quality of life of type 2 diabetes mellitus patients.*

Keywords: *questionnaire, validity, reliability, quality of life, diabetes mellitus.*

INTRODUCTION

Quality of life (QOL) is a multidimensional concept perceived by an individual based on his/ her culture and value systems, whether in good health or having disabilities/ chronic diseases, such as diabetes mellitus (DM).[1] The prevalence of DM was estimated to increase worldwide, including in Indonesia. International Diabetes Federation (IDF) estimated Indonesia will place seventh in 2045, with 16.7 million people estimated to have DM.[2] Previous studies showed that type 2 diabetes mellitus (T2DM) patients with symptoms and/ or complications had lower QOL compared to healthy individuals.[3,4]

The ultimate goal of T2DM management is to improve or preserve good QOL by maintaining adequate blood glucose control and managing comorbidities and complications.[5] Clinicians often use laboratory parameters to evaluate target of therapy, while parameters from patients' point of view, such as QOL, have not been elaborated much into management strategy even tough current guidelines have emphasized tailored therapy and patient's role in diabetes management.[5,6]

Quality of life is very subjective; therefore, socio-cultural background, demography, and ethnicities play major part in perceiving QOL.[7,8] Instruments to measure QOL have been developed as interest in this field grows, to name a few; WHO Quality of Life (WHOQOL), Short Form -36 (SF-36), Nottingham Health Profile (NHP), which measure QOL in general, and some instruments have been developed for specific disease such as Diabetes Quality of Life (DQOL) and Asian Diabetes Quality of Life (Asian DQOL).[7,9]

The development of Asian Diabetes Quality of Life (Asian DQOL) was first intended to overcome the issue of different cultural backgrounds and multi ethnicity in Malaysia, which were not conveyed by available quality of life measurement tools that were mostly developed based on Western population.[9] In line with this background, therefore this study selected Asian DQOL, which was considered to be the most relevant tools for Indonesian population, to be adapted into Indonesian language.

METHODS

Written permission to translate Asian Diabetes Quality of Life into Indonesian language was approved by the developer. Ethical approval was granted by Hasan Sadikin Hospital Health Research Ethics Committee (LB.02.01/ K6.5/342/2019). Written informed consent was obtained from all participants. This study consisted of translation and adaptation process followed by validity and reliability tests (**Figure 1**).

Translation and Adaptation

Translation and adaptation process was conducted in accordance with Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures which included six stages: initial translation, synthesis of the translations, back translation, review by group of experts, testing of pre-final version, and submission of documentation for appraisal of the adaptation process.[10] The initial drafts were translated by medical professionals and a certified linguist and discussed into joint draft. Back translation was done by native English translator. Review was conducted by group of experts consisted of two endocrinologists, two general internists, a general practitioner, and a certified linguist. The pre-final draft was appraised and tested, then the final draft was approved and given to study subjects.

Validity and Reliability Tests

The study was conducted in Endocrinology Clinic, Hasan Sadikin General Hospital, Bandung, Indonesia in November 2019 - January 2020. Out of 71 T2DM patients, using consecutive sampling, 65 patients were enrolled. The inclusion criteria were a patient who has been diagnosed with T2DM and aged 40-60 years, able to read and write, fluent in Indonesian language, and agrees to be enrolled in written consent. The exclusion criteria were a patient with psychiatric condition, hospitalized within 2 weeks, and having undergone routine dialysis. From 65 subjects, 5 were lost to follow up yielding 60 patients as study subjects.

Subjects were asked to fill in the final version of Indonesian Asian Diabetes Quality of Life. The result of the first test was not informed to

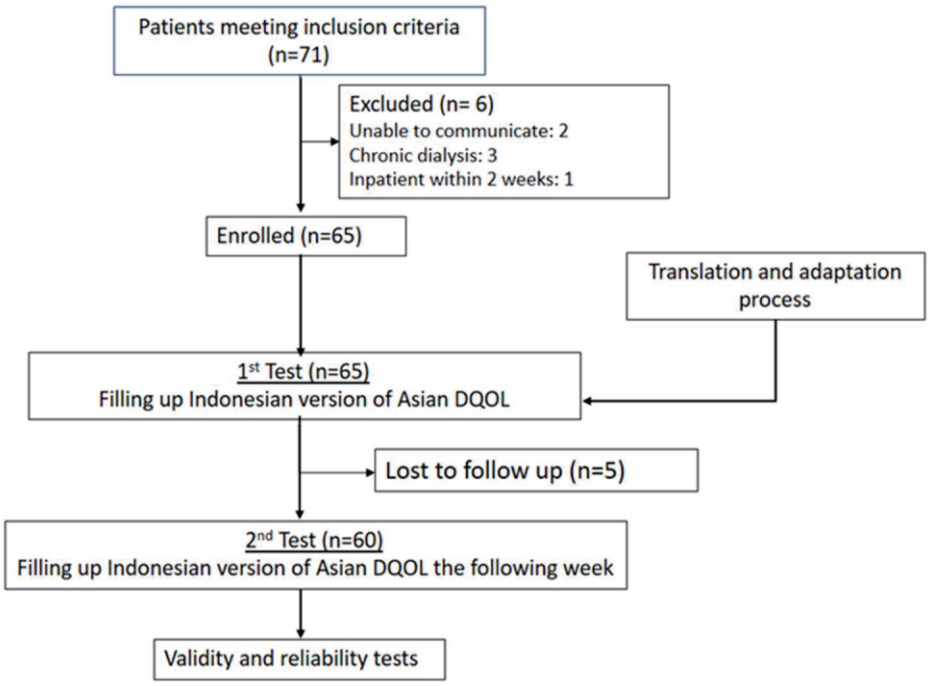

Figure 1. Study flow diagram.

the subjects. Subjects were then contacted to fill in again the questionnaire within 7-10 days. Results from both tests were analyzed to obtain validity and reliability.

Statistical Analysis

The study design was cross-sectional study. Correlation test between Likert scale of each question's answer and total score of all answers was conducted to determine convergent validity. Test-retest and internal consistency (Cronbach's alpha score) were done to determine reliability.[11,12] All statistical analysis was computed using SPSS version 25.0.

RESULTS

Subjects of this study were between 40-60 years old with median age of 54 years, 42 (70.0%) subjects were female, mainly were married (78.3%), of Sundanese ethnicity (71.6%), unemployed (61.7%), attended higher education (35.0%), and have been diagnosed with T2DM for 1-5 years (50.0%). Most prevalent comorbidities and complications found were peripheral neuropathy (63.3%), hypertension (60.0%), and dyslipidemias (53.3%). Majority of subjects were given insulin therapy (43.4%), had HbA1c level of 7-9.9% (57.1%), and with estimated glomerular filtration rate of > 60 ml/min/1.73 m^2 (65.5%).

Result of convergent validity test using Spearman's rank test showed that all questions across 5 domains had significant correlation (p-value < 0.05), therefore considered valid (**Figure 2**). Five out of six questions in diet domain had strong correlations (*r*: 0.61-0.75), only one question had moderate correlation (*r*: 0.50). All three questions in energy domain had very strong correlations (*r*: 0.85-0.89). Three out of four questions in memory domain had strong correlations (*r*: 0.65-0.78), and one had very strong correlation (*r*: 0.85). Financial aspect domain had five questions with three questions showing strong correlations (*r*: 0.67-0.79) and two had very strong correlations (*r*: 0.84; 0.86). Interpersonal relationship domain showed strong correlation (*r*: 0.78) on one question and very strong correlations (*r*: 0.93; 0.96) on two questions.

Reliability test by comparing the result of first and second test (test-retest) using Wilcoxon signed rank test (CI 95%) showed no difference between the consecutive tests (p-value > 0.05) (**Table 1**). Correlation test using Spearman's rank test showed that all domains had coefficient

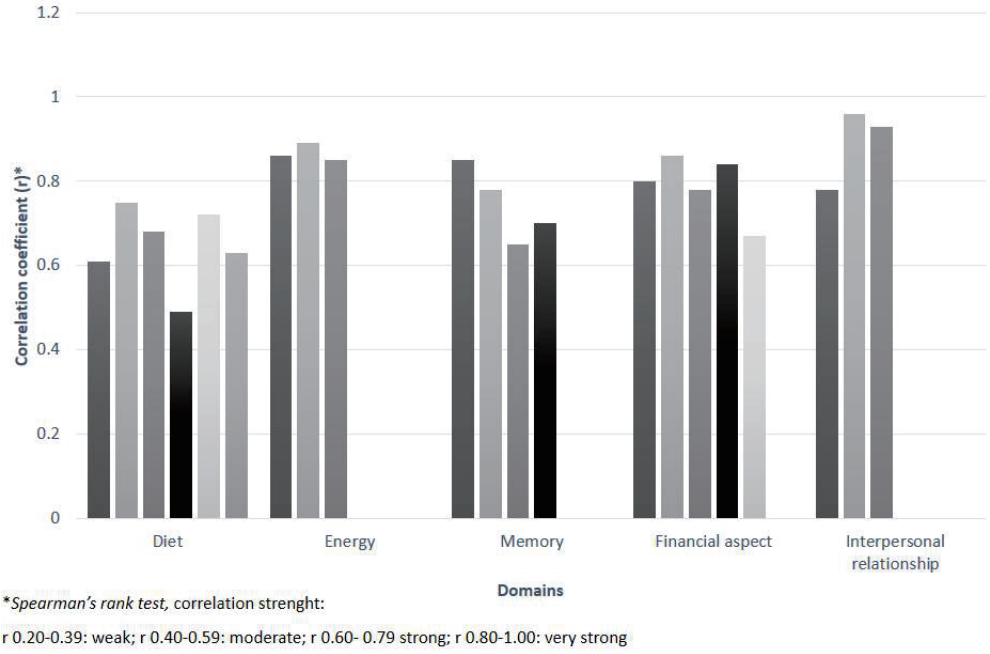

Figure 2. Convergent validity test result.

Table 1. Result of test-retest.

Domain	1st Test mean (SD)	2nd Test mean (SD)	p-value*	r**
Diet	22.583 (4.064)	22.917 (4.200)	0.059	0.93
Energy	10.900 (3.085)	11.033 (3.242)	0.591	0.84
Memory	17.483 (2.361)	17.683 (2.480)	0.083	0.91
Financial Aspect	19.367 (5.168)	19.517 (4.993)	0.310	0.98
Interpersonal relationship	9.978 (2.314)	10.085 (2.448)	0.695	0.83

SD = standard deviation, *Wilcoxon Signed Rank Test, **Spearman's rank correlation

Table 2. Internal consistency test result.

Domain	Number of questions (n)	Cronbach's alpha
Diet	6	0.756
Energy	3	0.863
Memory	4	0.793
Financial Aspect	5	0.879
Interpersonal relationship	3	0.906

Cronbach's alpha value:
≥ 0.9 : excellent; ≥ 0.8: good; ≥ 0.7: acceptable; ≥ 0.6: questionable; ≥ 0.5: poor;< 0.5: unacceptable.

correlation of more 0.70 (*r*: 0.83-0.98) surpassing the cut-off for reliability (**Table 1**). Internal consistency using Cronbach's alpha also showed all domains surpassed the acceptable score ≥0.70 (**Table 2**).

DISCUSSION

The development process of Asian DQOL included subjects from three different major ethnics in Malaysia (Malay, Chinese, and Indian) and was made in three languages: English, Malay, and Chinese (Mandarin); which were mainly used by this population. Five domains, including diet, energy, memory, financial aspect, and interpersonal relationship were found to have important value that affect quality of life of T2DM patients in Malaysia.[9] Experts discussion concluded that all five domains were also relevant

and important for Indonesian population.

In Indonesia eating also has high social value just like in other Asian countries where eating and dining play major part in family occasions, celebrations, and other cultural ceremonies or activities. Food has become means of social interactions and leisure, not merely just a necessity.[13,14] There is still common belief that food should always be finished as an attitude of gratitude and politeness. With this picture, it is understandable that diet restrictions could really affect patient's daily life. Energy and memory domains were considered to represent overall health status, therefore were relevant. Financial aspect still becomes source of worries in Indonesia even though most Indonesians are currently covered by government's health insurance system but there are some expenses not directly related to medical bills, such as transportation and accommodation expenses to reach health facilities, also loss of income when the person is sick or one must attend to sick family member. The topic of sexual life is still viewed as a taboo subject but as improvements of information openness, education, and health status ensue, this topic becomes current. Strong link between DM, erectile dysfunction, and poorer QOL has been found globally.[15,16]

**Countries with different socio-cultural backgrounds have different perspectives on quality of life; hence, the quality of life instruments used should omit or address different domains and be tailored to target population.[7] One example of quality of life questionnaire used in United States (US) is Diabetes Quality of Life (DQOL), which was composed by 60 questions, then was shortened into 15 questions. Both versions include four domains, which are satisfaction with treatment, impact of treatment, worry about the future effects of diabetes, and worry about social/vocational issues.[17] Domains selected in this questionnaire show that quality of life of T2DM patients in US is significantly affected by medical treatment of diabetes, while diet, medical expenses, and sexual life are of less concern.

There are numbers of quality of life instruments for T2DM patients in Europe with few variations depending on usage purpose. Most of the instruments were developed for certain research, therefore they are varied in certain questions with emphasis on different domains in accordance with research objectives. A systematic review by Levterova et al.[18] compared 14 diabetes quality of life instruments used in Europe and found that Audit of Diabetes-dependent quality of life (ADDQoL), Diabetes Care Profile (DCP), and Well-being Questionnaire (WBQ) had the best approach in measuring quality of life of diabetic patients in Europe. Questions in these instruments have several differences compared to Asian DQOL, where in these instruments, items on perception of treatment quality, patients' knowledge about diabetes, worry about pain and complications, limitations or disturbance in social life are addressed. European population perceived that time spent on diabetes treatment affected quality of life, whereas medical expenses were less worrisome. European patients also considered sleep and recreational activities as important parameters of quality of life.

Study by Huang et al.[14] aimed to develop quality of life instrument for diabetic patients in Taiwan, found that fitness and mobility were factors that strongly affect quality of life of diabetic patients in Taiwan. Huang et al. used several quality of life instruments, such as DQOL, D-39S, and RAND-12, that had been translated into Mandarin, as references. Huang et al. later added diet domain considering that eating had high social value and perceived as source of happiness in Taiwan, but omitted sexual life domain due to lack of validity and reliability of this domain. Illustrations above showed that population with different socio-cultural background will have different perception on quality of life.

Convergent validity analysis showed that Indonesian Asian DQOL had correlation coefficient ranges 0.50-0.75 for diet domain, 0.85-0.89 for energy domain, 0.65-0.85 for memory domain, 0.67-0.86 for financial aspect domain, and 0.78-0.95 for interpersonal relationship domain. This result was in line with the English version and Indonesian version. The English version had correlation coefficient ranges of 0.50-0.76, 0.56-0.87, 0.71-0.87, 0.80-0.904, and 0.67-0.88 consecutively. The Indonesian version

had correlation coefficient ranges of 0.52-0.77, 0.68-0.81, 0.95-0.84, 0.66-0.82, and 0.52-0.88 consecutively[9]. Both Indonesian and Bahasa version had the lowest correlation coefficient in diet domain and the strongest in interpersonal relationship domain.

Reliability test using test-retest showed no significant differences (p value < 0.05) and internal consistency showed Cronbach's alpha scores ≥ 0.07 for all domains. This result was consistent with the English version. Internal consistency of Indonesian version had Cronbach's alpha scores ≥ 0.07 for four domains with diet domain having Cronbach's alpha of 0.67[9], slightly lower than English and Indonesian version.

Limitation of this study was that most subjects had good education background (35.0% attended higher education. Moreover, 31.6% of study participants attended high school. There might be slight difference of interpretation towards Indonesian language in certain regions.

CONCLUSION

Indonesian Asian DQOL is a valid and reliable tool to measure quality of life of T2DM patients.

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Association of BsmI Polymorphisms in the Vitamin D Receptor Gene Among Indonesian Population with Diabetic Kidney Disease

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ABSTRAK

Latar belakang: *penyakit ginjal diabetik (PGD) sebagai penyebab utama penyakit ginjal tahap akhir (PGTA), merupakan komplikasi dari diabetes mellitus (DM). Salah satu kondisi yang menjadi faktor risiko PGD yaitu defisiensi vitamin D, dimana polimorfisme reseptor vitamin D (VDR) disinyalir memiliki peran. Studi ini bertujuan untuk melihat adanya hubungan antara polimorfisme reseptor vitamin D (VDR) terhadap PGD, dan faktor yang memengaruhi hubungan tersebut.* ***Metode:*** *studi dilakukan secara potong lintang pada pasien DM Tipe 2 di poliklinik Penyakit Dalam RSUPN Dr. Cipto Mangunkusumo, Jakarta dengan rentang waktu November 2014 – Maret 2015. Subjek yang memenuhi kriteria penelitian dilakukan pengumpulan data berupa karakteristik subjek, pemeriksaan fisik, dan pemeriksaan darah (polimorfisme BsmI gen reseptor vitamin D). Pasien dengan penyakit akut dan berat dieksklusikan dari studi. Selanjutnya dilakukan analisis secara bivariat dan multivariat antar variabel.* ***Hasil:*** *dari 93 subjek penelitian, didapatkan 42 (45.2%) subjek tanpa PGD dan 51 (54.8%) subjek dengan PGD. Sebagian besar subjek memiliki genotip Bb yaitu sebesar 89.2%, serta tidak ada subjek yang memiliki genotip BB. Sebagian besar subjek memiliki alel b, yakni sebesar 55.4%. Tidak terdapat hubungan yang berbeda bermakna antara polimorfisme BsmI gen reseptor vitamin D dengan PGD (OR = 1.243; CI 95% 0.334-4.621; p = 0.751).* ***Kesimpulan:*** *Genotip Bb pada polimorfisme BsmI didapatkan sebesar 89.2% dan genotip bb sebesar 10.8%. Sebagian besar subjek memiliki alel b, yakni sebesar 55.4%. Tidak ditemukan adanya hubungan bermakna antara polimorfisme BsmI gen reseptor vitamin D dengan PGD. Durasi DM lebih dari lima tahun memengaruhi hubungan antara kedua variabel tersebut.*

Kata kunci: *polimorfisme, BsmI, gen reseptor vitamin D, penyakit ginjal diabetik, ras Indonesia-Malay.*

ABSTRACT

Background: *Diabetic kidney disease (DKD), as a common cause of end-stage renal disease (ESRD), is a chronic complication of diabetes mellitus (DM). It has been established that vitamin D deficiency is one of DKD risk factors, which may be related to vitamin D receptor (VDR) polymorphisms. This study aimed to analyze the association between VDR polymorphisms and DKD in Indonesian population, also risk factors that influence it.* ***Methods:*** *a cross-sectional study was conducted in Type 2 DM patients who visited internal medicine outpatient clinic at Dr. Cipto Mangunkusumo Hospital, Jakarta, from November 2014 until March 2015. Data collection*

includes characteristics of subjects and laboratory examination, including BsmI polymorphisms in the vitamin D receptor gene. Patients with acute and severe disease were excluded from the study. Bivariate and multivariate analyses were done. ***Results:*** *of 93 DM subjects, 42 (45.2%) subjects were without DKD and 51 (54.8%) subjects had DKD. Most of the subjects had the Bb genotype (89.2%), with no subject having the BB genotype. The proportions of the B and b alleles were 44.6% and 55.4%, respectively. There is no association between BsmI polymorphisms in the vitamin D receptor gene and DKD (OR = 1.243; CI 95% 0.334-4.621; p value = 0.751).* ***Conclusion:*** *the profile of BsmI polymorphisms in the vitamin D receptor gene in the Indonesian population were genotypes Bb (89.2%) and bb (10.8%). There was no association between BsmI polymorphisms in the vitamin D receptor gene and DKD. Duration of DM more than five years influenced the association between those variables.*

Keywords: *polymorphisms, BsmI, vitamin D receptor (VDR) gene, diabetic kidney disease, Indonesian–Malay race.*

INTRODUCTION

Diabetic kidney disease (DKD) is a common cause of end-stage renal disease (ESRD). Data from the Indonesian Renal Registry (2011) revealed that the 25% etiology of patients who have undergone hemodialysis is DKD.[1] Factors that are associated with DKD include blood glucose control, hypertension, dyslipidemia, duration of diabetes mellitus (DM), high body mass index, age, sex, ethnicity, vitamin D deficiency, high-sodium diet, high-protein diet, and smoking.[2–7]

Vitamin D has an anti-calcium effect by inhibiting the renin-transcription process, angiotensin II, the renal-inflammation process, and albumin excretion. It also prevents podocyte damage, glomerulosclerosis, and transformation from kidney epithelial cells into mesenchymal cells.[8] Current studies on the association between vitamin D deficiency and DKD are still controversial. Those controversial results may be related to genetic factors, which are vitamin D receptor (VDR) polymorphisms. The VDR polymorphism is affected by the *Cdx2, ApaI, BsmI, FokI,* and *TaqI* genes, whereas the Asian population is mostly affected by *ApaI, FokI*, and *Cdx2*.[9]

Several studies have reported the association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD in various populations. Zhang et al. (2012) study revealed an association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD in Han Chinese population, while Vedralova et al. (2012) study in Caucasians showed the opposite result.[10,11] However, the association between *BsmI* polymorphism in the vitamin D receptor gene and DKD has not been investigated in the Indonesian population. Based on the current evidence, we aimed to analyze the association between *Bsml* polymorphism in the vitamin D receptor gene and DKD particularly in Indonesian population. In terms of secondary objective, we aimed to investigate other risk factors that influence the association between main variables. By knowing the potential risk factor of *BsmI* polymorphism in the vitamin D receptor gene, it is hoped that the number of cases and morbidity of DKD can be prevented.

METHODS

A cross-sectional study was conducted to understand the association of *BsmI* polymorphisms in the vitamin D receptor gene with DKD among the Indonesian–Malay race. The subjects of this study were patients who came to the internal medicine outpatient clinic, Dr. Cipto Mangunkusumo Hospital, Jakarta, from November 2014 until March 2015. The inclusion criteria were patients with type-2 DM, of Indonesian–Malay population, who signed the informed consent form. Patients with urinary tract infection or fever, who were pregnant or in their menstrual period, had undergone hemodialysis or peritoneal dialysis, had used nonsteroid anti-inflammatory drugs (NSAIDs), and postexercise were excluded. This study has been approved by the Ethical Committee

of Faculty of Medicine Universitas Indonesia (Reference no. 756/UN2.F1/ETIK/2014).

Data collection included subjects' characteristics, physical examination, and laboratory examination, including *BsmI* polymorphisms in the vitamin D receptor gene. 5 mL of venous blood was collected in a non-fasting state and added to an EDTA-anticoagulated container. BsmI polymorphisms were measured using polymerase chain reaction with high resolution melt analysis. Since the diabetic kidney disease was defined from albuminuria, the mid-stream random urine was collected in a urine collector. Albuminuria was measured using *Nyocacard U-albumin* with sandwich immunometric assay technique.

The data were then analyzed by SPSS v.16. Participants' characteristics were reported in percentages for categorical data, mean (standard deviation), or median (range) for continuous data. A chi square test was used to analyze the association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD. Also, logistic regression analysis was performed to investigate the role of other risk factors that influence the association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD. Bivariate and multivariate analyses were presented with confidence interval 95% and considered statistically significant if the p value was <0.05.

RESULTS

93 subjects were recruited for the present study. There were 51 subjects (54.8%) with DKD and 42 subjects (45.2%) without DKD. The characteristics of the subjects, which include demography and laboratory examination results, are presented in **Table 1**.

Table 1. Characteristics of the subjects.

	DKD (n = 51)	Without DKD (n = 42)
Sex, n (%)		
- Male	28 (66.7)	14 (33.3)
- Female	23 (45.1)	28 (54.9)
Age, median (range)	61 (46-73)	61.5 (45–85)
Body mass index (kg/m^2), mean (SD)	26.08 (3.93)	25.40 (3.84)
Duration of DM, n (%)		
- > 5 years	39 (63.9)	22 (36.1)
- ≤ 5 years	12 (37.5)	20 (62.5)
Systolic BP (mmHg), median (range)	137 (88–180)	130 (98–173)
Diastolic BP (mmHg), median (range)	74 (52–100)	75 (51–94)
eGFR (mL/min/1.73 m^2), mean (SD)	43.46 (22.46)	73.51 (23.23)
Urea (mg/dL), median (range)	39 (17–145)	25.5 (13–54)
Creatinine (mg/dL), median (range)	1.5 (0.7–9.6)	0.9 (0.6–1.9)
Fasting blood glucose mg/dL), median (range)	133 (79–365)	121.5 (75–285)
2-hours postprandial blood glucose (mg/dL), median (range)	199 (60–521)	180.5 (80–479)
HbA1c (%), median (range)	7.5 (5.4–11.1)	7.2 (5.9–11.4)
Total cholesterol (mg/dL), mean (SD)	187.35 (44.66)	175.48 (35.34)
Triglyceride (mg/dL), median (range)	115.5 (30–447)	95.5 (52–272)
HDL cholesterol (mg/dL), mean (SD)	50.57 (18.77)	53.57 (12.76)
LDL cholesterol (mg/dL), mean (SD)	117.88 (40.46)	108.00 (29.47)

DKD: Diabetic kidney disease; DM: Diabetes mellitus; BP: Blood pressure.

The proportion of Genotype and Allele of *BsmI* Polymorphisms in Vitamin D Receptor Gene are presented in **Table 2**. The majority of the subjects had the Bb genotype (89.2%), and no subject had the BB genotype. The percentage of the b allele was 55.4%.

Table 2. Genotype and allele of the subjects.

	Frequency n (%)
Genotype	
- Bb	83 (89.2)
- bb	10 (10.8)
Allele	
- B	83 (44.6)
- b	103 (55.4)

Association of *BsmI* Polymorphisms in Vitamin D Receptor Gene with DKD

There is no association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD (OR = 1.234; CI 95% 0.334–4.621; p = 0.75). There is also no significant association between allele B or allele b on *BsmI* polymorphisms in the vitamin D receptor gene and DKD (OR = 1.043; CI 95% 0.584–1.866; p = 0.89). (**Table 3** and **Table 4).**

Risk Factors of DKD

Several factors have significant associations with DKD, such as duration of DM being more than five years (p value = 0.015), blood

Table 3. Association of BsmI polymorphisms in vitamin D receptor gene with DKD.

	DKD n (%)	Without DKD n (%)	Total n (%)	OR	95% Confidence Interval	
					Min	Max
Bb	46 (55.4)	37 (44.6)	83 (100)	1.243	0.334	4.621
bb	5 (50)	5 (50)	10 (100)			

Table 4. Association between B allele of BsmI polymorphisms in vitamin D receptor gene and DKD.

	DKD n (%)	Without DKD n (%)	Total n (%)	OR	95% Confidence Interval	
					Min	Max
B	46 (55.4)	37 (44.6)	83 (100)	1.043	0.584	1.866
b	56 (54.4)	47 (45.6)	103 (100)			

Table 5. Risk factors of DKD.

	DKD n (%)	Without DKD n (%)	OR	95% Confidence Interval	
				Min	Max
Genotype					
- Bb	46 (55.4)	37 (44.6)	1.243	0.334	4.621
- bb	5 (50)	5 (50)			
Duration of DM					
- > 5 years	39 (63.9)	22 (36.1)	2.955	1.218	7.167
- ≤ 5 years	12 (37.5)	20 (62.5)			
Body mass index					
- Overweight and Obese	40 (59.7)	27 (40.3)	2.020	0.806	5.062
- Normal	11 (42.3)	5 (57.7)			
Blood pressure					
- Hypertension	48 (62.3)	29 (37.7)	7.172	1.883	27.319
- Without hypertension	3 (18.8)	13 (81.2)			
Blood glucose control					
- Uncontrolled	40 (55.6)	32 (44.4)	1.023	0.378	2.769
- Controlled	11 (55)	9 (45)			
Dyslipidemia					
- Dyslipidemia	28 (57.1)	21 (42.9)	1.217	0.537	2.760
- Without Dyslipidemia	23 (52.3)	21 (47.7)			
Blood pressure control					
- Uncontrolled	23 (62.2)	14 (37.8)	1.643	0.705	3.829
- Controlled	28 (50)	28 (50)			
Kidney function					
- eGFR < 60	41 (75.9)	13 (24.1)	9.146	3.531	23.690
- eGFR ≥ 60	10 (25.6)	29 (74.4)			

pressure (p value = 0.001), and kidney function (p value < 0.001). From logistic regression analysis, confounding factors had effects on the association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD with crude OR of 1.243 (95% CI 0.334–4.621) and adjusted OR of 1.410 (95% CI 0.335–2.296). Duration of DM being more than five years influenced the association of *BsmI* polymorphisms in the vitamin D receptor gene and DKD. The results are presented in **Table 5** and **Table 6**.

Table 6. Crude OR and Adjusted OR Genotype as Risk Factor of DKD and Effect from Other Risk Factors

	OR	95% CI	
Genotype Bb	Crude OR: 1.243	0.334–4.621	
Adjusted			
(+) eGFR	1.137	0.248–5.216	8.5%
(+) Hypertension	1.058	0.219–5.121	6.9%
(+) Duration of DM	1.449	0.278–7.551	37%
(+) Body Mass Index	1.525	0.283–8.217	5.2%
(+) BP Control	1.410	0.260–7.652	7.5%

DISCUSSION

The studied participants were type-2 DM patients who came to the Internal Medicine Outpatient Clinic, Dr. Cipto Mangunkusumo Hospital, Jakarta. Most of the subjects were female with ages ranging from 45 to 85 years old. Dewi et al.[12] study and Indra et al.[13] study showed similar participants; most of their subjects were female. The duration of DM of most subjects was more than five years (65.6%), and most subjects had comorbidities, such as hypertension, elevated body mass index, and dyslipidemia. These findings resembled Indra et al.[13] study, which had 82.8% patients with hypertension and most of them with more than five years' duration of DM. Insulin resistance in type-2 DM patients causes an increase in angiotensin II, inflammatory mediator release, which causes endothelial damage, and hyperglycemia, which increases sodium reabsorption in renal tubules. Hence, plasma volume will increase, which leads to hypertension.[14]

Even though hypertension was the major comorbidity among type-2 DM patients in this study, the median blood pressure in both groups was less than 140/90 mmHg, since 81.7% of subjects had already taken antihypertensive drugs such as ACE inhibitors or ARBs. More than half of the participants belonged to the DKD group (54.8%). This finding was related to the higher number of patients with comorbidities such as hypertension, dyslipidemia, overweight, poor glycemic control (HbA1c median = 7.45), and more than five years of DM. A total of 82.8% subjects had a higher body mass index, with a mean of 26.08 from the DKD group and 25.40 from the non-DKD group. It was found that obesity leads to oxidative stress conditions, which cause endothelial damage and decrease adiponectin levels. Such conditions result in renal podocyte damage.[15]

Most subjects with DKD had an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 (75.9%). Albuminuria in DKD causes reduced renal function by triggering chemokine expression and activating complements of renal tubules, which cause infiltration of inflammatory cells in interstitial and fibrogenesis. In the end, reduced renal function may have resulted in an ESRD state.[16]

Based on the results of this study, 10.8% of the subjects had the bb genotype, 89.2% had the Bb genotype, and none had the BB genotype. There were 44.6% subjects with the B allele and 55.4% with the b allele. This result was different from Zhang et al.[10] study, which showed the majority of the bb genotype among the participants. On the other hand, Vedralova et al.[11] showed the BB genotype for most of the patients. Based on these previous studies, it can be concluded that genotype differences are influenced by race. Indonesian native citizens, most of whom come from the Malay race, are different from Han Chinese, who belong to the Mongoloid race, and are also different from the Caucasian race.

Data suggested an elevated number of DKD among BB genotypes (adjusted OR 1.410), but the confidence interval was above 1 (CI 95% 0.260–7.652). This result contradicted Zhang et al. (2012),[10] who revealed a significant correlation between *BsmI* polymorphisms in the vitamin D receptor gene and DKD among Han

Chinese population.

Besides *BsmI*, vitamin D receptor polymorphism was influenced by other investigated genes, such as *TaqI, ApaI*, and *FokI.* Zhang et al.[10] study conducted among Han Chinese population stated that there is no association between *ApaI* polymorphisms in the vitamin D receptor gene and DKD in the same population. A study from Arababadi et al. (2010) found that there was no significant association between *ApaI* and *TaqI* polymorphisms and DKD. Arababadi et al. (2010) found that vitamin D receptor gene polymorphisms have an association with DM, but not with DKD.[17] Vedralova et al.[11] also found that the vitamin D receptor-gene polymorphism that has an association with DKD is *FokI*.

In the case of the separation of alleles B and b, no significant association was found between the B allele of *BsmI* polymorphisms in the vitamin D receptor gene and DKD (p value = 0.89). This result was different from Zhang et al.[10] study, which found that allele B has a significant association with DKD among Han Chinese population. According to logistic regression analysis, more than five years' duration of DM has the greatest influence on the association of *BsmI* polymorphisms in the vitamin D receptor gene and DKD. Another study also reported that a longer duration of DM increases the prevalence of DKD and increases the proteinuria.[18]

To the best of our knowledge, this is the first study to analyze the proportion and association of *BsmI* polymorphisms in vitamin D receptors with DKD in the Indonesian–Malay race. This study provides a preliminary understanding of vitamin D receptor-gene polymorphisms and the influence of genetic factors in the therapeutic response of DKD. However, this study lacks the measurement of both vitamin D and vitamin D receptor levels of the subjects which might affect the association between variables. Hence, there were several confounding factors affecting the association between the *BsmI* gene-receptor vitamin D and DKD. Also, this study analyzed only the association of the *BsmI* gene as one of the vitamin D receptor-gene polymorphisms. Therefore, this study was not able to describe the entirety of vitamin D receptor-gene polymorphisms. This still warrants further studies.

CONCLUSION

The profiles of *BsmI* polymorphisms in the vitamin D receptor gene in the Indonesian–Malay race were genotypes Bb (89.2%) and bb (10.8%). There was no association between *BsmI* polymorphisms in the vitamin D receptor gene and DKD, which might be due to the influence of genetic factors among different populations. In addition, the duration of DM being more than five years influenced the association between those variables.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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Frequency of Acute Kidney Injury in Patient Receiving Piperacillin - Tazobactam: A Hospital-based Study from Qatar

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ABSTRAK

Latar belakang: *beberapa penelitian telah melaporkan acute kidney injury (AKI) terkait piperacillin-tazobactam (TAZ/PIPC) dengan berbagai frekuensi. Tujuan dari penelitian ini adalah menentukan frekuensi AKI terkait TAZ/PIPC di antara pasien kami dan untuk mengidentifikasi faktor risiko pada entitas klinis.* ***Metode:*** *penelitian potong lintang retrospektif ini dilakukan di Rumah Sakit Umum Hamad; melibatkan pasien dewasa yang dirawat dari Januari 2017 hingga Desember 2017.* ***Hasil:*** *terdapat 917 pasien yang diikutsetakan, di antaranya 635 (69,25%) laki-laki dan 282 (30,75%) perempuan. Usia rerata pasien adalah 52 (SB 19) tahun, dan 98 (10,7%) pasien didiagnosis dengan AKI. Para pasien dengan AKI secara signifikan lebih tua daripada tanpa AKI [59,71 (SB 19,79) versus 51,06 (SB 18,67); P <0,001]. Setelah inisiasi TAZ/PIPC, rerata kadar kreatinin pada kelompok AKI lebih tinggi dibandingkan rerata kadar kreatinin pada kelompok non-AKI, [158,91 (SB 81,93) berbanding 66,78 (SB 21,42); P<001]. Rerata waktu timbulnya AKI setelah inisiasi PIPC/TAZ adalah 4,46 (SB 3,20) (1-12 hari). AKI secara signifikan terkait dengan albumin serum rata-rata rendah (P<0,001), gula darah puasa rerata tinggi (P<0,001), penyakit arteri koroner (P<0,001), gagal jantung (P<0,001), penyakit hati (P=0,047), diabetes melitus (P=0,021) dan hipertensi (P<0,001). Angka mortalitas di rumah sakit secara signifikan lebih tinggi pada kelompok AKI [38,78% berbanding 5,13% pada kelompok non-AKI; P<0,001], dan hanya usia lanjut dan gagal jantung yang ditemukan sebagai faktor risiko independen untuk AKI terkait TAZ/PIPC.* ***Kesimpulan:*** *TAZ/PIPC secara signifikan berhubungan dengan AKI. Usia lanjut dan gagal jantung diidentifikasi sebagai faktor risiko independen untuk AKI terkait TAZ/PIPC.*

Kata kunci: *acute kidney injury, piperacillin/tazobactam, usia lanjut, gagal jantung.*

ABSTRACT

Background*: several studies have been reported piperacillin-tazobactam (TAZ / PIPC)-associated AKI with various frequencies. The aim of this study was to determine the frequency of TAZ/PIPC- associated AKI among our patients and to identify the risk factors for this clinical entity.* ***Methods:*** *this retrospective cross-sectional study was conducted at Hamad General Hospital; it involved adult patients who were admitted from January 2017 to December 2017.* ***Results:*** *we involved 917 patients, of whom 635 (69.25%) were males and 282 (30.75%) were females. The mean age of the patients was 52 (SD 19) years, and 98 (10.7%) patients were diagnosed with AKI. The patients with AKI were significantly older than without AKI [59.71 (SD 19.79) versus 51.06 (SD 18.67); P <0.001]. After TAZ/PIPC initiation, the mean creatinine level in the AKI group was higher than the*

mean creatinine level in the non-AKI group, [158.91 (SD 81.93) versus 66.78 (SD 21.42); P<001]. The mean time of onset of AKI after PIPC/TAZ initiation was 4.46 (SD 3.20) (1-12 days). AKI was significantly associated with low mean serum albumin (P<0.001), high mean fasting blood glucose (P<0.001), coronary artery diseases (P<0.001), heart failure (P<0.001), liver diseases (P=0.047), diabetes mellitus (P=0.021) and hypertension (P<0.001). The in-hospital mortality was significantly higher in the AKI group [38.78% versus 5.13% in the non-AKI group; P<0.001], and only advanced age and heart failure were found as independent risk factors for TAZ/PIPC-associated AKI. ***Conclusion:*** *TAZ/PIPC was significantly associated with AKI. Advanced age and heart failure were identified as independent risk factors for TAZ/PIPC-associated AKI.*

Keywords: *acute kidney injury, piperacillin/tazobactam, advanced age, heart failure.*

INTRODUCTION

The combination piperacillin-tazobactam (TAZ/PIPC) is a commonly prescribed empirical therapy for patients with healthcare-associated infections, as it provides coverage against both methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Pseudomonas aeruginosa*.[1]

Common adverse effects include headache, trouble sleeping, itching, skin rash, nausea, leucopenia, neutropenia, constipation, and diarrhea.[1] Serious adverse effects include Clostridioides difficile infection and allergic reactions including anaphylaxis may occur.[2,3] Acute kidney injury (AKI) as an adverse effect of TAZ/PIPC has been mentioned in several reports with varying frequencies. The proposed mechanisms for TAZ/PIPC induced AKI include acute interstitial nephritis or toxic effects on the renal tubule.[4-5]

During our practice, we noted that many patients developed AKI after using TAZ /PIPC; however, the frequency of this complication in our hospital is unknown. This study was designed to determine the frequency of AKI due to TAZ/PIPC among our patients and to identify the risk factors for TAZ/PIPC-associated AKI.

METHODS

This retrospective analytical cross-sectional study was conducted at Hamad General Hospital (HGH), which is a tertiary center that covers all specialties except for hematology-oncology and obstetrics. This study involved adult patients who were admitted to HGH from January 1, 2017 to December 31, 2017 and received piperacillin-tazobactam at a dose of 4.5 g intravenously every eight hours daily.

Inclusion and Exclusion Criteria

Eligible subjects were adults of 18 years of age or more, who were admitted to HGH from January 1, 2017 to December 31, 2017, and received piperacillin-tazobactam at a dose of 4.5 g intravenously every eight hours daily. Patients younger than 18 years old and patients who had a baseline serum creatinine level of ≥1.2 mg/dl (106 mcmol/L) [3] or receiving renal replacement therapy at the time of the initiation of treatment, were excluded. Moreover, patients who had recent administration of contrast agents also were excluded.

Source of Data and Data Collection

The list of the patients who received TAZ/PIPC from January 1, 2017 to December 31, 2017 was obtained from the pharmacy electronic records at HGH. Then the electronic medical records (Cerner system) of all patients were screened for inclusion purposes and the records of the eligible patients were reviewed to obtain demographic data, Laboratory data (baseline serum creatinine, serum creatinine after receiving TAZ/PIPC, fasting blood glucose and serum albumin), comorbidities (hypertension, CAD, DM, COPD, PAD, heart failure, liver disease, active cancer), concomitant drugs (NSAIDS, ACE/ARB, vancomycin, acyclovir, diuretics), type of infection and the outcome.

Outcomes

The primary outcome of our study was acute kidney injury (AKI), which was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) criteria, [6] as an increase in serum creatinine level by 50% or higher from baseline or by 0.3 mg/dL (26.5 μmol/L) or higher within 2 hospital days or

fewer. The secondary outcome was in-hospital mortality, which was defined as all deaths occurring during the hospital stay.

Data Analysis

Results were expressed as mean ± SD. After the demonstration of a normal distribution, two-tailed unpaired Student's t-tests and the Mann-Whitney test were used to compare the distribution of quantitative variables and the $\chi 2$ tests and Fisher's test for categorical variables. Variables that showed significant association in bivariate analysis (P<0.05) were entered into multivariate analysis to identify the independent risk factors of AKI at P<0.05.

Ethical Approval

The ethical approval for this study was obtained from the medical research committee (MRC) at Hamad Medical Corporation (HMC). The reference to the approved proposal was MRC-01-18-065. According to the MRC, a waiver of informed consent is not required for any retrospective study and all data/samples were fully anonymized by the principal investigator and other team members before being accessed by others including the biostatistician, journal and readers.

RESULTS

During the study period, we retrospectively identified 2540 patients who received TAZ/PIPC, of which 917 fulfilled the inclusion criteria and became the subject of this study as illustrated in **Figure 1**. The electronic medical records of all eligible patients were fetched and reviewed. Of the 917 patients, there were 635 (69.25%) males and 282 (30.75%) females. The mean age of the patients was 52 SD 19 (range:18-90 years) and 98 (10.7%) patients were found to have acute kidney injury (AKI). **Table 1** describes the demographic and clinical data of the cohort of this study.

A Comparison between AKI and Non-AKI Groups

The patients with AKI were significantly older than without AKI [59.71 (SD 19.79) vs 51.06 (SD 18.67); P <0.001]. After TAZ/PIPC initiation, the mean creatinine level in the AKI group was higher than the mean creatinine level in the non-AKI group, [158.91 (SD 81.93) versus 66.78 (SD 21.42); P<001]. The mean time of onset of AKI after PIPC/TAZ initiation was 4.46 (SD 3.20) (1-12 days). AKI was significantly associated with low mean serum albumin (P<0.001), high mean fasting blood glucose (P<0.001), coronary artery diseases (P<0.001), heart failure (P<0.001), liver diseases (P=0.047), diabetes mellitus (P=0.021) and hypertension (P<0.001). The in-hospital mortality was

Table 1. Demographic and Clinical Characteristics of the Patients Involved in This Study.

Characteristics	Number (%) / Mean (SD)
Sex, n (%)	
- Female	282 (30.75)
- Male	635 (69.25)
Age (years), mean (SD)	51.98 (18.97)
BMI, mean (SD)	27.04 (6.73)
Nationalities, n (%)	
- Non-Qatari	640 (69.79)
- Qatari	277 (30.21)
CAD, n (%)	130 (14.18)
PAD, n (%)	36 (3.93)
COPD, n (%)	39 (4.25)
Heart failure, n (%)	63 (6.87)
Liver disease, n (%)	53 (5.79)
DM, n (%)	378 (41.22)
Hypertension, n (%)	360 (39.3)
Active cancer, n (%)	107 (11.67)
Hematology cancer, n (%)	24 (2.62)
NSAID, n (%)	142 (15.49)
ACEI/ARB, n (%)	181 (19.74)
Vancomycin, n (%)	100 (10.91)
Acyclovir, n (%)	20 (2.18)
Diuretics, n (%)	169 (18.43)
Pneumonia, n (%)	406 (44.27)
Endocarditis, n (%)	1 (0.11)
Febrile neutropenia, n (%)	24 (2.62)
Urinary tract, n (%)	96 (10.47)
Abdominal infection, n (%)	181 (19.74)
Musculoskeletal, n (%)	107 (11.67)
Septicemia, n (%)	183 (19.98)
Others, n (%)	131 (14.3)
AKI, n (%)	98 (10.7)
Baseline creatinine, mean (SD)	69.50 (17.75)
Creatinine after TAZ/PIPC initiation, mean (SD)	76.63 (43.93)
Duration of TAZ/PIPC therapy, mean (SD)	6.13 (4.17)
Duration of TAZ/PIPC until AKI, mean (SD)	4.46 (3.20)
Albumin, mean (SD)	27.38 (6.46)
Fasting blood glucose, mean (SD)	7.58 (3.53)
AKI duration, mean (SD)	10.93 (18.73)
Renal replacement therapy, n (%)	17 (1.9)
In-hospital mortality, n (%)	80 (8.72)

Table 2. Comparison between AKI group and non-AKI group in relation to demographic, clinical characterestics of patients involved in this study.

Characteristics	Total (N=917)	AKI Negative (N=819)	AKI Positive (N=98)	P-value
Age, mean (SD)	51.98 (18.97)	51.06 (18.67)	59.71 (19.79)	<0.001
Male, n (%)	635 (69.25)	573 (69.96)	62 (63.27)	0.174
Qatari, n (%)	277 (30.21)	242 (29.55)	35 (35.71)	0.209
BMI, mean (SD)	27.04 (6.73)	26.89 (6.62)	28.29 (7.45)	0.051
Baseline creatinine, mean (SD)	69.50 (17.75)	67.84 (17.20)	83.33 (16.29)	<0.001
Creatinine after TAZ/PIPC initiation	76.63 (43.93)	66.78 (21.42)	158.91 (81.93)	<0.001
Duration of TAZ/PIPC, mean (SD)	6.13 (4.17)	6.07 (4.24)	6.75 (3.53)	0.268
Albumin, mean (SD)	27.29 (6.99)	27.60 (6.98)	24.75 (6.59)	<0.001
Fasting blood glucose, mean (SD)	7.58 (3.53)	7.4 (3.37)	9.07 (4.38)	<0.001
Coronary artery disease (CAD), n (%)	130 (14.18)	103 (12.58)	27 (27.55)	<0.001
Peripheral artery disease (PAD), n (%)	36 (3.93)	31 (3.79)	5 (5.1)	0.526
COPD, n (%)	39 (4.25)	35 (4.27)	4 (4.08)	0.929
Heart failure, n (%)	63 (6.87)	41 (5.01)	22 (22.45)	<0.001
Liver disease, n (%)	53 (5.79)	43 (5.26)	10 (10.2)	0.047
Diabetes mellitus, n (%)	378 (41.22)	327 (39.93)	51 (52.04)	0.021
Hypertension, n (%)	360 (39.3)	302 (36.92)	58 (59.18)	<0.001
Active cancer, n (%)	107 (11.67)	92 (11.23)	15 (15.31)	0.235
Hematology cancer, n (%)	24 (2.62)	19 (2.32)	5 (5.1)	0.103
NSAID, n (%)	142 (15.49)	131 (16.0)	11 (11.22)	0.217
ACEI/ARB, n (%)	181 (19.74)	159 (19.41)	22 (22.45)	0.476
Vancomycin, n (%)	100 (10.91)	79 (9.65)	21 (21.43)	<0.001
Acyclovir, n (%)	20 (2.18)	19 (2.32)	1 (1.02)	0.405
Diuretics, n (%)	169 (18.43)	121 (14.77)	48 (48.98)	<0.001
Pneumonia, n (%)	406 (44.27)	348 (42.49)	58 (59.18)	0.002
Endocarditis, n (%)	1 (0.11)	1 (0.12)	0 (0)	0.729
Febrile neutropenia, n (%)	24 (2.62)	22 (2.69)	2 (2.04)	0.705
Urinary tract, n (%)	96 (10.47)	84 (10.26)	12 (12.24)	0.543
Abdominal infection, n (%)	181 (19.74)	174 (21.25)	7 (7.14)	0.001
Musculoskeletal, n (%)	107 (11.67)	98 (11.97)	9 (9.18)	0.418
Septicemia, n (%)	183 (19.98)	152 (18.58)	31 (31.63)	0.002
In-hospital mortality, n (%)	80 (8.72)	42 (5.13)	38 (38.78)	<0.001

significantly higher in the AKI group [38.78% versus 5.13% in the non-AKI group; $P<0.001$]. Table 2 summarizes the conditions associated with AKI in this study.

The Outcomes and the Independent Risk Factors for AKI

The in-hospital mortality was 80 (8.72%). **Table 3** describes the outcomes of the cohort of this study. After adjusting the relationship to include many variables, and by using conditional multiple logistic regression analysis, only advanced age (adjusted OR=0.96, 95% CI = 0.93-1.00, P= 0.03) and heart failure (adjusted OR=3.8, 95%CI=1.16-12.54, P=0.02) were found to be independent risk factors for AKI (**Table 4**).

Table 3. Outcomes of the cohort of this study.

Outcomes	N (%)
Creatinine after TAZ/PIPC initiation, mean (SD)	76.63 (43.93)
AKI, n (%)	98 (10.7)
AKI duration, mean (SD)	10.93 (18.73)
Renal replacement therapy, n (%)	17 (1.9)
In-hospital mortality, n (%)	80 (8.72)

DISCUSSION

TAZ / PIPC is one of the most commonly used antibiotics in our hospital. Its effectiveness is attributed to its ability to cover broad-spectrum gram-negative microorganisms and anaerobic agents. At the time of introduction to our hospital, it was an unrestricted antibiotic that allowed any physician to prescribe the antibiotic indefinitely.

Table 4. Results of multivariate analysis of predictors of AKI.

Variables	Adjusted OR	P value
Age	0.96 (0.93-1.00)	0.038
Baseline creatinine	0.98 (0.96-1.01)	0.214
Creatinine after TAZ/ PIPC initiation	1.03 (1.00-1.06)	0.079
Albumin	1.00 (0.94-1.06)	0.951
Fasting blood glucose	0.96 (0.86-1.07)	0.474
CAD	1.51 (0.51-4.48)	0.460
Heart failure	3.80 (1.16-12.45)	0.027
Liver disease	1.54 (0.40-5.89)	0.531
Diabetes mellitus	0.36 (0.12-1.08)	0.069
Hypertension	1.57 (0.49-4.98)	0.447
Vancomycin	0.47 (0.14-1.58)	0.219
Diuretics	0.63 (0.25-1.62)	0.342
Pneumonia	1.48 (0.62-3.52)	0.371
Abdominal infection	0.35 (0.09-1.35)	0.128
Septicemia	2.49 (0.94-6.59)	0.065
In-hospital mortality	1.56 (0.47-5.19)	0.467

However, because of its high prescription volume and rising expenses[1], a restriction decision has been made in the last three years till present, in an attempt to monitor and control the judicious use of this antibiotic. As part of a stewardship program in Hamad Medical Corporation (HMC), TAZ/PIPC was placed on a 48-hour restriction, therefore, any physician could order the antibiotic, but each order would be given a 48-hour stop date, after which it is subjected to a review by an infectious disease physician.

To our knowledge, this is the first study to report TAZ/PIPC-associated AKI among patients treated in Hamad General Hospital, Qatar. We think our results will support the efforts of the stewardship program designers to restrict the use of this antibiotic in HMC to avoid unwanted side effects such as AKI that results from the judicious use of this antibiotic.

Regardless of the characteristics of the population analyzed and the criteria used to diagnose AKI, TAZ / PIPC-associated AKI has been reported by several authors with various frequencies; the estimated frequency varies between 7.8 and 38.5% of cases.[3-9] In our study, the frequency of TAZ/PIPC-associated AKI was 10.7% of cases, which falls within the international range. TAZ/PIPC is often co-administered with vancomycin to cover methicillin-resistant Gram-positive organisms in various infections such as catheter-related bloodstream infections. It has recently been reported that patients receiving a combination of vancomycin and TAZ / PIPC had a relatively high AKI level compared to patients receiving vancomycin alone.[3,4,10-13] Although our study was not designed to compare between patients who used vancomycin in combination with TAZ/PIPC and patients who received TAZ/PIPC alone, the number of patients who received vancomycin in the AKI group was significantly higher than the patient in the non-AKI group [21 (21.43%) vs. 79 (9.65%); P<0.001], which is in keeping with the above studies. Based on this finding, patients receiving a combination of vancomycin and TAZ

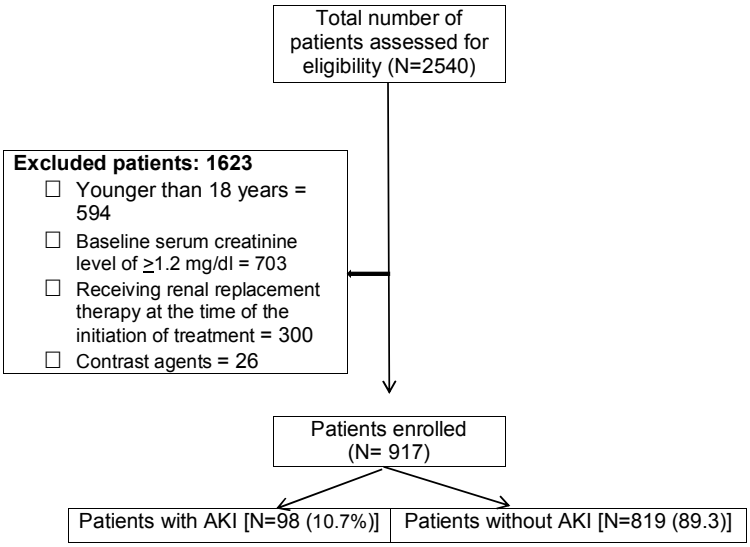

Figure 1. A flow chart of patients recruitment in this study

/ PIPC should, therefore, be closely monitored for the development of AKI and it would be better if they were switched to a less nephrotoxic regimen. Moreover, we found that the AKI group used more diuretics than the non-AKI group [48 (48.98%) vs. 121 (14.77%); P<0.001], which is contrary to a report by Rutter et al.[4] The exact mechanism of AKI in these patients is unclear. However, this finding indicates that we should use TAZ/PIPC cautiously in patients under diuretics.

Of note, the duration of TAZ/PIPC use was significantly longer in the AKI group than in the non-AKI group [7.44 (SD 6.09) vs. 6.04 (SD 4.24); P=0.004], which coincide with other reports in the literature.[14] Therefore, we support the stewardship program recommendation on the restriction of TAZ/PIPC, as this step will shorten the duration of exposure of the patients to this drug. Our study also showed a significant association between AKI and many variables such as low serum albumin, diabetes mellitus, coronary artery disease, liver disease, pneumonia, abdomen infection, sepsis and hypertension. In critically ill patients with sepsis, AKI is a recognized clinical entity; in one study,[15] it was found in 66% of patients admitted to the intensive care unit. In such a case, AKI may be a consequence of the sepsis itself or of therapeutic interventions that include drugs like vancomycin and TAZ/ PIP, or the dual effect of both. In the same context, Jensen et al. observed that in patients with sepsis-related renal dysfunction, exposure to TAZ/ PIP is associated with a lower rate of improvement in glomerular filtration rate (GFR) compared to other antibiotics and that the kidney function improves rapidly after stopping this medication.[16] Given this finding, let us conclude that patients with sepsis are more susceptible to AKI if they receive TAZ/ PIP. Further prospective RCTs are needed to confirm this observation. However, it is advisable to look for effective strategies to reduce nephrotoxicity in this group of patients. Suggested strategies include avoiding dehydration and co-administration of other nephrotoxic agents. Other actions include close monitoring of renal function, early and repeated reevaluations of empirical antibiotic therapy with appropriate alterations, and the use of alternatives to TAZ/PIP such as cefepime or an antipseudomonal carbapenem.[17] On the other hand, the reason for the significant association between AKI and hypertension in patients receiving TAZ/PIP is unclear, however, it could be attributed to the pre-existing hypertensive renal disease.

Interestingly, we only found advanced age and heart failure to be associated significantly with AKI in both bivariate and multivariate analyses. The association of advanced age and heart failure with AKI in patients receiving TAZ/ PIPC could be explained by the fact that heart failure and advanced age cause reduced renal blood flow[13,14] that may aggravate tubular injury related to TAZ/PIPC, by limiting oxygen and nutrient availability and facilitating oxidative stress. We, therefore, recommend caution when using TAZ/ PIPC in patients with advanced age and heart failure who should be closely monitored for the development of AKI. To our knowledge, this is the first clinical study to report heart failure as an independent risk factor for AKI associated with TAZ/PIPC administration.

A noteworthy finding of this study is that the in-hospital mortality was higher in AKI patients compared to non-AKI patients [38 (38.78%) vs. 24 (5.13%); p = 0.02], which is consistent with emerging evidence suggesting that there are higher in-hospital mortality rates with even smaller changes in serum creatinine level.[18] However, the impact of TIZ/PIP-associated AKI on mortality is unclear due to the lack of information and the paucity of studies.

Our study has several limitations. First, it was a retrospective study that did not allow us to study in detail many variables, such as the reason for the prolonged use of TAZ/ PIPC in some patients in our study over a period of up to 42 days. Moreover, we did not have detailed information about other medications used during the study period. Second, we have excluded patients under the age of 18 years. As a result, we missed the opportunity to estimate the prevalence of TAZ/ PIPC-induced AKI among different groups in our hospital. Third, we did not have the facilities to measure TAZ/ PIPC levels to assess whether patients with AKI had higher

TAZ/ PIPC blood levels or not. Fourth, This was a hospital-based study, despite the large sample size, therefore, the results may not be applicable to other hospitals.

CONCLUSION

We found that TAZ/PIPC was associated with AKI and that co-administration of TAZ/ PIPC with vancomycin or diuretics resulted in a high rate of AKI compared to patients receiving TAZ/PIPC alone. Advanced age and heart failure have been identified as independent risk factors for TAZ/PIPC-induced AKI that should be targeted to prevent AKI and improve patient outcomes. We, therefore, recommend baseline evaluation and continuous monitoring of renal function in high-risk patients receiving TAZ/ PIPC therapy.

CONFLICT OF INTEREST

There is no conflict of interest.

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The Correlation Between HbA1c and Neuropathy Disability Score in Type 2 Diabetes

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ABSTRAK

Latar belakang: *World Health Organization (WHO) memperkirakan angka kejadian DM tipe 2 di Indonesia sebesar 21.3 juta jiwa pada tahun 2030. Diabetes Melitus mempunyai komplikasi kronis. Salah satu komplikasi kronis adalah terjadinya neuropati perifer. Untuk mengetahui terjadinya neuropati, pemeriksaan fisik yang direkomendasikan adalah menilai Neuropathy Disability Score (NDS). Haemoglobin A1c (HbA1c) adalah glycated haemoglobin yang digunakan untuk menilai status kadar gula dalam 2 atau 3 bulan terakhir. Hubungan antara HbA1C dengan derajat keparahan neuropati DM dilakukan dengan pemeriksaan elektrodiagnostik menunjukkan bahwa peningkatan kadar HbA1c dan usia menjadi prediktor utama terjadinya neuropati DM namun pemeriksaan elektrodiagnostik mahal. Untuk itu diperlukan penelitian untuk mengetahui hubungan antara kadar HbA1c dengan NDS sehingga morbiditas neuropati DM dapat diminimalisir. Penelitian ini bertujuan untuk mengetahui hubungan antara derajat keparahan neuropati diabetes yang diukur dengan Neuropathy Disability Score dengan nilai HbA1c pada penderita diabetes melitus tipe 2.* ***Metode*****:** *penelitian analitik korelatif dengan metode cross sectional. Setiap penderita DM yang memenuhi kriteria inklusi dan eksklusi dimasukkan sampai jumlah sampel terpenuhi. Data yang terkumpul dianalisis dengan uji korelasi Spearman.* ***Hasil:*** *didapatkan 56 subyek penelitian. Rerata usia 59.55 (SB 9.48) dengan 57.1% berjenis kelamin wanita, median lamanya menderita DM 5.5 tahun. Median nilai skor NDS sebesar 7.5 dan median nilai HbA1c sebesar 8.65. Analisa korelasi Spearman menunjukkan koefisien korelasi sebesar 0.487 dengan nilai p=0.000.* ***Kesimpulan:*** *terdapat hubungan antara kadar HbA1c dengan derajat keparahan neuropati pada pasien DM tipe 2.*

Kata Kunci*: Haemoglobin A1c, neuropati, diabetes melitus.*

ABSTRACT

Background: *World Health Organization (WHO) estimates the incidence of type 2 diabetes in Indonesia would increase to 21.3 million in 2030. Diabetes has a chronic complications, including peripheral neuropathy. The degree of neuropathy was assessed through the Neuropathy Disability Score (NDS). In contrast, haemoglobin A1c is glycated haemoglobin used to monitor the glucose levels of diabetic patients in the last 2 or 3 months. The relationship between HbA1c and diabetic neuropathy carried out by electrodiagnosis showed that HbA1c and age were the main predictors of diabetic neuropathy. However, electrodiagnosis is still considered costly. Research is needed to determine the relationship between HbA1c and NDS to reduce morbidity. This study aims to determine the relationship between the severity of diabetic neuropathy as measured by NDS with HbA1c*

level in type 2 Diabetes. ***Methods:*** *this cross-sectional study involved correlation analysis.. The collected data were analyzed with the Spearman correlation test.* ***Results:*** *approximately 56 diabetic patients were involved in this study. Patients were recruited from the internal medicine outpatient ward from the West Nusa Tenggara General Hospital. The mean age was 59.55 (SD 9.48) with 57.1% female; the median duration of diabetes was 5.5 years. The median NDS score is 7.5 and the median HbA1c value is 8.65. Spearman correlation analysis shows a correlation coefficient of 0.487 with a value of p = 0.000* ***Conclusion:*** *there is a relationship between HbA1c level and the severity of diabetic neuropathy in Type 2 DM.*

Keywords: *Haemoglobin A1c, neuropathy, diabetes mellitus.*

INTRODUCTION

Based on the International Diabetes Federation, 425 million people would suffer from Diabetes Mellitus (DM) by 2045. In a developing country, including Indonesia, it is predicted that 4 out of 5 have Diabetes.[1] According to the Basic Health Research conducted by the Ministry of Health Indonesia in 2013, DM is the 4th most non-communicable disease after cancer in Indonesia. Furthermore, in West Nusa Tenggara, the estimated number of people having DM is 0.9% of the total population.[2]

Diabetes is a metabolic disease with an abnormal hyperglycemic index that occurs due to abnormal insulin secretion, insulin action, or combined. DM type 2 has several classic symptoms, including polyuria, polydipsia, polyphagia, and weight loss. DM diagnosis requires several laboratory examinations: fasting blood glucose level, 2 hours after postprandial blood glucose level, and Haemoglobin A1c (HbA1c).[3] Diabetes Mellitus has several acute and chronic complications that may affect various organs and cause morbidity and mortality. Chronic complications are categorized into vascular (microvascular and macrovascular) and non-vascular complications. Microvascular complications include neuropathy, nephropathy, and retinopathy, whereas macrovascular complications include cerebrovascular, coronary heart disease, and peripheral arterial disease.[4]

DM neuropathy affects 50% of people with both type 1 and type 2 DM. Diabetic neuropathy can be in the form of polyneuropathy, mononeuropathy, or autonomic neuropathy. The occurrence of neuropathy is related to the duration of DM and control of blood glucose. The most type of neuropathy is distal symmetric polyneuropathy and the most common symptoms are such sensory disorders as hyperesthesia, paresthesia, and dysesthesia.[4] To identify the complications of neuropathy in diabetes, it is necessary to screen and then stratify for the degree of neuropathy. Screening the occurrence of neuropathy is conducted through a series of questions to patients to find out whether there is neuropathy. A series of physical examinations such as the Neuropathy Disability Score (NDS) can be used to determine the degree of neuropathy so that complications can be prevented. NDS include pinprick examination, Achilles reflex examination, temperature, and vibration perception on patients.[5,6] NDS examination is performed on both sides and a score ≥ 6 points are considered abnormal.[6]

Haemoglobin A1c (HbA1c) is glycated haemoglobin used to monitor the status of glucose levels in the previous 2 or 3 months. Recommendation from the American Diabetes Association (ADA), HbA1c levels must be maintained at 7% in all diabetics patients. HbA1c levels above 7% increase the risk of complications, especially microvascular complications. Koening and colleagues first reported the relationship between HbA1c and blood glucose control in uncontrolled diabetic patients. Many studies indicate an association between HbA1c and diabetes complications. However, few studies have focused on HbA1c levels with diabetic polyneuropathy.[7] Early detection of diabetes polyneuropathy can prevent morbidity. Neuropathy Disability Score (NDS) has been widely accepted and validated as an assessment tool to identify the presence of diabetic neuropathy.[8] The relationship between HbA1c and the severity of diabetic neuropathy is

done by electrodiagnosis examination, showing that increased HbA1c levels and age are the main predictors of diabetes neuropathy.[9] The electrodiagnosis examination is a sophisticated examination and not all hospitals in low resource settings have this device so that validated physical testing is needed to establish the severity of the diabetic neuropathy.[9] For this reason, research is required to explore the correlations between HbA1c and the severity of diabetic neuropathy as assessed by the Neuropathy Disability Score (NDS) among diabetes mellitus patients.

METHODS

This cross-sectional study was conducted from March to August 2019 with criteria of type 2 diabetes mellitus who experienced neuropathy symptoms selected by examining neuropathy symptom scores. Patients were recruited from the internal medicine outpatients ward of West Nusa Tenggara General Hospital. Patients who experience symptoms of neuropathy were examined for neuropathy disability scores and HbA1c levels. Neuropathy disability scores include vibration sensation with a 128 Hz tuning fork, temperature sensation with a cold tuning fork, pinprick examinations, and Achilles reflex examinations on both sides of the body (**Table 1**). The maximum NDS score is 10 and the abnormal score is ≥ 6.[6]

Table 1. Neuropathy disability score (NDS).[6]

NDS Items	Description
Vibration Sensation (128 Hz tuning fork)	0 = present, 1 = reduced/absent per side
Temperature sensation (cold tuning fork)	0 = present, 1 = reduced/absent per side
Pin-prick	0 = present, 1 = reduced/absent per side
Ankle reflex	0 = present, 1 = present with reinforcement, 2 = absent per side

This study has been approved by the Ethical Committee of Mataram University (Reference number 41/UN18.F7/ETIK/2019).

In this study, a minimum sample of 51 patients was determined and sampling was carried out by the method according to the case that came sequentially (sampling from consecutive admission) until a predetermined sample size was reached. Data were analyzed through the Pearson correlation test or Spearman if the requirements for the Pearson correlation test were not obtained. All data were analyzed using SPSS version 22.0.

RESULTS

Fifty-six individuals met the criteria of this study, see **Table 2**. The mean age of the study subjects was 59.55 (SD 9.48) years. The youngest patient was 43 years old and the oldest was 79 years old. Demographic data of research subject are shown in **Table 2**.

Table 2. Baseline characteristic (n: 56).

Characteristic	Value	p
Age (years), mean (SD)	59.55 (9.48)	0.757
Sex, n		0.396
- Male	24	
- Female	32	
Type of therapy, n		
- Medical	36	
- Insulin	15	
- Others	5	
Length of diabetes, mean (SD)	6.95 (5.07)	0.238
NDS value, mean (SD)	6.77 (2.55)	
HbA1c value, mean (SD)	9.13 (2.36)	

The correlation between NDS values and HbA1c levels was tested with the Spearman correlation test because the data were not normally distributed even though the data transformation was done. From the Spearman correlation test results obtained a correlation coefficient of 0.487 with a value of p = 0.000 (**Table 3**)

Table 3. Correlation of HbA1c with NDS.

Variable	Coefficient correlation	*p*	n
NDS vs HbA1c	+ 0,487	0,000	56

Spearman correlation test

DISCUSSION

Research subjects were predominantly female. This was similar to the previous study in China showing that DM in women was mostly found in rural area and male in urban areas.[10] Based on age, the mean age of study subjects was 59.55 (SD 9.48) years. The CDC (*Centers for Disease Control and Prevention*) report shows the average age of DM sufferers was 53.8 years

in 1997 and 54.2 years in 2011. Furthermore, previous studies reported that the average age of DM in Hong Kong was 52 years and in China was 40-59 years.[10]

Patients with DM for more than five years have a higher risk of neuropathy. The results of this study indicate that the median duration of DM is 5.5 years. Reports in the United Kingdom (UK), DM neuropathy, occurs in 36% of people with diabetes for more than ten years compared with people with diabetes less than five years and nerve denervation damage increases with the length of DM.[11]

Various scores were developed to assess the degree of neuropathy in people with DM. One of the score that are often used is NDS (*Neuropathy Disability Score*). The median value of NDS in the study was 7.5. NDS assesses Achilles reflexes, vibration sensations, prick pin tests, and temperature sensations on both feet with a maximum score of 10 where a score of 6 or more indicates a severe degree of neuropathy. Data reports in the UK show that 50% of people with DM show neuropathy symptoms and 7% have diabetic foot after 1 year.[12]

This study aims to find the relationship between DM neuropathy severity by measuring the NDS scale with HbA1c levels. Spearman correlation analysis results show there is a significant relationship between HbA1c and NDS. This indicates that the higher the HbA1c value in patients with type 2 DM, the higher the NDS value was. In other words, the higher the HbA1c level, the higher the severity of the neuropathy. Zilliox *et al*.[11] research showed that NDS values in DM neuropathies were 6.26 (SD 0.34). The electrodiagnosis examination found in patients with large fiber neuropathy showed a heavier NDS value compared to patients with small fiber neuropathy [(7.23 (SD 0.91) vs 4.77 (SD 0.53)]. The research of Stem *et al*.[12] showed that complications of DM (neuropathy, retinopathy, or nephropathy) occur in patients with HbA1c 8.5 (SD 1.5). The higher levels of HbA1c will further accelerate and worsen the complications of neuropathy. Control of glucose levels is very important to prevent and decrease the complications from DM. High levels of HbA1c have associated with high microvascular complications in people with DM. Limitations of this study were HbA1c was only evaluated once and electrodiagnosis examination was not performed as a gold standard to determine the severity of neuropathy.

CONCLUSION

HbA1c level is related to the severity of neuropathy in patients with type 2 diabetes. The higher the HbA1c value, the higher the Neuropathy Disability Score. Monitoring of HbA1c level is crucial to prevent further complications of DM both in the nervous system and in other organs.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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The Risk Factors of Multidrug-Resistant Organisms in Hospitalized Patients with Community-Acquired Pneumonia in Dr. Soetomo Hospital Surabaya, Indonesia

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ABSTRAK

Latar belakang: *multidrug-resistant organisms (MDRO) penyebab pneumonia merupakan kasus yang krusial. Infeksi MDRO menjadi masalah utama pada community-acquired pneumonia (CAP). Beberapa faktor berperan terhadap terjadinya infeksi MDRO pada CAP. Tujuan penelitian ini adalah menganalisis MDRO sebagai etiologi pasien CAP rawat inap beserta faktor risikonya di RSUD Dr. Soetomo sebagai salah satu rumah sakit rujukan di Indonesia Timur.* ***Metode:*** *penelitian ini merupakan observasional analitik dengan kohort retrospektif, dilakukan pada Januari 2016 sampai Desember 2018. Data dikumpulkan dari rekam medis pasien. Diagnosis Cepat Otomatis (Phoenix TM) digunakan sebagai metode standar untuk uji kultur dan kepekaan. Beberapa faktor risiko dianalisis terhadap terjadinya infeksi MDRO.* ***Hasil****: lima patogen yang umum ditemukan pada pasien CAP rawat inap adalah Acinetobacter baumannii 244/1364 (17,9%), Klebsiella pneumoniae 134/1364 (9,8%), Pseudomonas aeruginosa 91/1364 (6,7%), Escherichia coli 58/1364 (4,3%), dan Enterobacter cloacae 45/1364 (3,3%). Terdapat 294/1364 (21,5%) MDRO yang diisolasi dari pasien CAP. Infeksi MDRO berhubungan dengan riwayat rawat inap sebelumnya, malignansi, penyakit kardiovaskular, dan penyakit paru struktural dengan nilai p masing-masing 0,002, <0,001, 0,024, dan <0,001.* ***Kesimpulan****: insiden MDRO pada CAP tinggi (21,5%). Faktor risiko yang berhubungan adalah riwayat rawat inap sebelumnya, malignansi, penyakit kardiovaskular, dan penyakit paru struktural.*

Kata kunci**:** *faktor risiko, multidrug-resistant organisms, community-acquired pneumonia.*

ABSTRACT

Background: *multidrug-resistant organisms (MDRO) caused pneumonia has become a crucial case. MDRO infection has been a problem concern to community-acquired pneumonia (CAP). A lot of factors play roles in CAP with MDRO infection. This study aimed to analyze MDRO as the etiology of hospitalized patients with CAP along with its risk factors in Dr. Soetomo Hospital as one of the top referral hospitals in east Indonesia.* ***Methods:*** *this retrospective cohort study was conducted from January 2016 to December 2018. Data were collected from patients' medical records. Automatic Rapid Diagnosis (Phoenix TM) was used as a standard method for culture and susceptibility test. Various risk factors were analyzed for MDRO infection.* ***Results:*** *five most common pathogens in hospitalized patients with CAP were Acinetobacter baumannii 244/1364 (17.9%), Klebsiella pneumoniae 134/1364 (9.8%), Pseudomonas aeruginosa 91/1364 (6.7%), Escherichia coli 58/1364 (4.3%), and Enterobacter cloacae 45/1364 (3.3%). There were 294/1364 (21.5%) MDROs isolated from patients with CAP. MDRO infection was linked to previous hospitalization, malignancy, cardiovascular disease,*

and structural lung disease with p values of 0.002, <0.001, 0.024, and <0.001, respectively. ***Conclusion:*** *the incidence of MDRO in CAP is high (21.5%). The risk factors related were previous hospitalization, malignancy, cardiovascular disease, and structural lung disease.*

Keywords: *risk factors, multidrug-resistant organisms, community-acquired pneumonia.*

INTRODUCTION

Multidrug-resistant organism (MDRO) is defined as pathogens which are resistant to one or more class of antimicrobial agents and often to all but one or two commercial antimicrobial agents. Concerning examples are such as carbapenem-resistant *Enterobacteriaceae* (CRE), multidrug-resistant *Acinetobacter baumannii,* extended spectrum beta-Lactamase-producing Gram-negative bacilli (ESBLs), Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Staphylococcus aureus* (VISA/VRSA), Vancomycin-resistant *Enterococci* (VRE), and multidrug-resistant *Streptococcus pneumonia* (MDRSP).[1]

MDROs infections have become a serious issue to community-acquired pneumonia (CAP). Based on hospital data from low and middle-income countries (LMIC), the total incidence of community-acquired extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae* infections is increasing progressively.[2,3]

Patients with MDRO infection have a higher risk of hospitalization, higher costs, require a longer duration of being hospitalized, and negatively affect the clinical outcomes.[4-6] The risk factors of the MDR infections are antimicrobial therapy in the previous 90 days, being hospitalized for the last 5 days or more, high rates of antibiotic resistance in the community or the particular hospital unit, and immunosuppressive disease and/or therapy.[7] Other variables may play roles in the incidence of MDRO. There are only a few data explaining the risk factors for MDRO isolation in CAP. However, concern for the presence of these pathogens drives the physicians to prescribe an empiric broad-spectrum antibiotic for CAP. Lately, the idea of MDRO has gained lots of attention during the past decade in both literature and clinical practice. Pneumonia cases in the community, which caused by MDRO, show a real and emerging problem.

According to American Thoracic Society (ATS) guideline (2005), healthcare-associated pneumonia (HCAP) includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; residence in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.[7] In the 2016 ATS guideline, HCAP could be included in the upcoming CAP guidelines because patients with HCAP, like those with CAP, frequently present from the community and are initially cared for in the emergency department. The consideration of HCAP to be included as CAP was due to the reported studies that many patients with HCAP are not at high risk for MDR pathogens and although interaction with the healthcare system is potentially a risk for MDR pathogens, underlying patient characteristics are also important independent determinants of risk for MDR pathogens.[8] In community-acquired pneumonia, it was important to identify the proportion of MDRO as the etiology, especially in Indonesia. This study aimed to analyze MDRO as the etiology of hospitalized patients with CAP patients along with its risk factors in Dr. Soetomo Hospital as one of the top referral hospitals in east Indonesia.

METHODS

This was a retrospective observational analytic study with a cohort design, conducted at the Dr. Soetomo Hospital in Surabaya, Indonesia. Data were collected from patients' medical records. The number of sample was adjusted to the number of CAP cases with complete medical records. The study population was 1,441 patients diagnosed with CAP. Considering the invalid

data or incomplete medical records, the final sample was 1,364 patients.

All patients aged 18 years and older, and diagnosed with CAP from January 2016 to December 2018 were included in the study. Patients with incomplete medical records' were excluded. Automatic rapid diagnosis (Phoenix TM), conducted at microbiology laboratory in Dr. Soetomo General Hospital, was used as a standard method of culture and susceptibility testing in CAP patients.

Pneumonia was defined as the existence of pulmonary opacity in chest x-ray during inpatient treatment which relates to more than one of the following signs and symptoms: (1) new or worsened cough with or without sputum production; (2) fever (37.8 ^{0}C) or hypothermia (35.6 ^{0}C); or abnormal number of white blood cell (leucopenia or leukocytosis), or the value of C-reactive protein beyond the local upper limit.

Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community as compared to the healthcare system. CAP is commonly defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute opacity on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/ or localized rales), in a patient not hospitalized or residing in a long-term care facility for ≥14 days before onset of symptoms. Symptoms of acute lower respiratory infection may include several (in most studies, at least 2) of the following: fever or hypothermia, rigors, sweats, new cough with or without sputum production or change in color of respiratory secretions in a patient with chronic cough, chest discomfort, or the onset of dyspnea. Most patients also have nonspecific symptoms, such as fatigue, myalgias, abdominal pain, anorexia, and headache.[9]

In this study, previous hospitalization was defined as previous inpatient treatment in the previous 90 days before the onset of symptoms and not being hospitalized for ≥14 days before the onset of symptoms. MDRO was defined as pathogens which resistant to one or more classes of antimicrobial agents, and usually to all commercially available antimicrobial agents, saving one or two agents. MDRO Criteria used in this study was from a standardized international terminology describing acquired resistance profile by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC).[10] Methicillin-resistant Staphylococcus aureus (MRSA) and all pathogens which are resistant to ≥1 agent in ≥3 antimicrobial categories were considered to be MDR pathogens in this study. Antimicrobial categories used in this study were aminoglycosides, carbapenems, cephalosporins, antipseudomonal penicillin + β-lactamase inhibitors, penicillin + β-lactamase inhibitors, tetracyclines, glycylcyclines, fluoroquinolones, monobactams, and phosphonic acids.

Variables evaluated as the possible risk factors were age, previous hospitalization, malignancy, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular disease, renal failure, structural lung disease. A variety of risk factors variables were analyzed for MDRO infection. Underlying diseases were regarded as active co-morbid if the signs or symptoms appeared or if the patients received treatment for the diseases. Renal failure was determined when the creatinine was >2 mg/dl or twice the baseline creatinine in a patient with chronic renal failure. Cardiovascular failure was determined when inotropic drugs were required, and hepatic failure was determined when bilirubin level was >2 mg/dl.

All variables in this study were categorical variables. Chi-square test or Fisher's exact test was used for statistical analysis. Variables with $p<0.25$ were included in multivariate logistic regression. Statistical result was considered significant if the p-value was <0.05. SPSS 21.0 was used for the statistical analysis.

This study was approved by the Institutional Review Board/ Ethics Committee review, with the approval number of 295/Panke.KKE/IV/2017 on 19 April 2017.

RESULTS

Of 1,441 patients with CAP, 77 (5.3%) of them did not have complete medical records and were excluded from the study. We collected complete data of 1,364 patients diagnosed with CAP, see **Table 1**.

Of the 1,364 patients with CAP, 84 (6.2%) had negative sputum cultures, 490 (35.9%) had normal flora and the isolated pathogens were 790 (57.9%). The five most common pathogens isolated were *Acinetobacter baumannii* with 244 (30.9%), followed by *Klebsiella pneumoniae* with 134 (17%), *Pseudomonas aeruginosa* with 91 (11.5%), *Escherichia coli* with 58 (7.3%), and *Enterobacter cloacae* with 45 (5.7%). This result is presented in **Table 2**.

Of the 1,364 patients with sputum culture data, there were 294 (21.6%) MDRO in this study as presented in **Table 3**. The five most common MDR pathogens were MDR *Acinetobacter baumannii,* MDR *Klebsiella pneumonia,* MDR *Escherichia coli,* MDR *Pseudomonas*

Table 1. Demography of CAP patients (N=1,364) in Dr. Soetomo Hospital on January 2016 to December 2018.

	N (%)		Total
	MDRO	Non MDRO	
Sex			
- Male	176 (21.1)	660 (78.9)	836
- Female	118 (22.3)	410 (77.7)	528
Age, Mean (SD)	51.08 (17.435)	51.55 (16.255)	51.45 (16.511)
Age range			
- >65 years old	64 (24.2)	201 (75.8)	265
- ≤65 years old	230 (20.9)	869 (79.1)	1099

CAP: Community-acquired pneumonia; MDRO: multidrug-resistant organism.

Table 2. The pathogens profile of sputum culture method (N=790) of CAP patients in Dr. Soetomo Hospital, from January 2016 to December 2018.

Isolated organisms	Count (N)	Percentage (%)
Acinetobacter baumannii	244	30.9
Klebisiella pneumoniae	134	17.0
Pseudomonas aeruginosa	91	11.5
Escherichia coli	58	7.3
Enterobacter cloacae	45	5.7
Stenotrophomonas maltophilia	23	2.9
Streptococcus pneumoniae	18	2.3
Enterobacter aerogens	8	1.0
Staphylococcus aureus	8	1.0
Pseudomonas putida	8	1.0
Other respiratory tract bacteria	153	19.4

CAP: Community-acquired pneumonia.

Table 3. Bacterial profile in MDRO.

MDR Pathogens	N (294)	Percentage
MDR *Acinetobacter baumannii*	106	36.1
MDR *Klebsiella pneumoniae*	80	27.2
MDR *Escherichia coli*	43	14.6
MDR *Pseudomonas aeruginosa*	25	8.5
MDR *Enterobacter cloacae*	19	6.5
MDR *Enterobacter aerogens*	4	1.4
MDR *Stenotrophomonas maltophilia*	3	1.0
MDR *Staphylococcus aureus*	2	0.7
Other MDR Pathogens	12	4.1

MDRO: Multidrug-resistant organism; MDR: Multidrug-resistant.

aeruginosa, and MDR *Enterobacter cloacae*. Other MDR pathogens were MDR *Serratia marcescens,* MDR *Acinetobacter spp,* MDR *Citrobacter freundii,* MDR *Kluyvera intermedia,* MDR *Burkholderia cepacia,* MDR *Pantoea agglomerans,* MDR *Enterococcus raffinosus.*

Of the 1,364 patients, there were 294 (21.6%) MDRO and 1,070 (78.4%) non-MDRO. According to **Table 4**, variables associated with developing MDRO were previous hospitalization, malignant disease, cardiovascular disease, and structural lung disease with p values of 0.002, <0.001, 0.024, and <0.001.

Variables with a P<0.02 based on Chi-square or Fisher's exact test were entered into a multivariate logistic regression model using binary regression binary logistic. Logistic regression showed that malignancy and structural lung disease were both associated with a 2-fold increased risk of MDRO infection (**Table 5**).

DISCUSSION

Our study found 1,364 patients with community-acquired pneumonia (CAP), consisting of 836 (60.3%) men and 528 (38.7%) women. The mean age was 51.45 years. Patients age >65 years old were 265 (19.4%) and age ≤65 years old were 1099 (80.6%). Previous study found that the risk of pneumonia increases as the increases of age. Vinogradova et al.[11] reported that among 17,172 cases of pneumonia, there were 47.3% patients age ≥65 years old.

Of the 1,364 patients with CAP, 84 (6.2%) were negative in sputum culture and 490 (35.9%) were normal flora. Another study found a

Table 4. The risk factors of patients who developed community-acquired pneumonia in Dr. Soetomo Hospital, from January 2016 to December 2018.

Variables		MDRO (n=294/21.6%)	Non MDRO (n=1,070/78.4%)	P Value
		N (%)	N (%)	
Age	Age >65 y.o (n=265)	64 (24.2)	201 (75.8)	0.252
	Age ≤65 y.o (n=1099)	230 (20.9)	869 (79.1)	
Renal Failure	With Renal Failure (n=32)	8 (25.0)	24 (75.0)	0.631
	No Renal Failure (n=1332)	286 (21.5)	1046 (78.5)	
Diabetes Mellitus	With Diabetes Mellitus (n=160)	37 (23.1)	123 (76.9)	0.607
	No Diabetes Mellitus (n=1204)	257 (21.3)	947 (78.7)	
COPD	With COPD (n=56)	10 (17.9)	46 (82.1)	0.492
	No COPD (n=1308)	284 (21.7)	1024 (78.3)	
Hepatic Failure	With Hepatic Failure (n=46)	13 (28.3)	33 (71.7)	0.260
	No Hepatic Failure (n=1318)	281 (21.3)	1037 (78.7)	
Cardiovascular Disease	With cardiovascular Disease (n=158)	45 (28.5)	113 (71.5)	0.024
	No Cardiovascular Disease (n=1206)	249 (20.6)	957 (79.4)	
Previous Hospitalization	With Previous Hospitalization (n=648)	163 (25.2)	485 (74.8)	0.002
	No Previous Hospitalization (n=716)	131 (18.3)	585 (81.7)	
Malignancy	With Malignancy (n=140)	49 (35)	91 (65)	<0.001
	No Malignancy (n=1224)	245 (20)	979 (80)	
Structural Lung Disease	With Structural Lung Disease (n=102)	40 (39.2)	62 (60.8)	<0.001
	No Structural Lung Disease (n=1262)	254 (20.1)	1008 (79.9)	

Based on chi-square test or Fisher's exact test. MDRO: Multidrug-resistant organism; COPD: chronic obstructive pulmonary disease.

Table 5. Multivariate analysis of risk factors for MDRO infection in CAP patients.

Variables	P	OR	95% CI
Previous Hospitalization	<0.001	1.737	1.320-2.286
Malignancy	<0.001	2.134	1.455-3.131
Cardiovascular Disease	0.006	1.744	1.174-2.591
Structural Lung Disease	<0.001	2.816	1.833-4.327

MDRO: Multidrug-resistant organism; CAP: Community-acquired pneumonia; OR: odds ratio.

higher number of negative bacterial cultures of sputum in pneumonia with 131 (78.44%) and 61 (61%).[12,13] Of the 790 pathogens, five most common were *Acinetobacter baumannii* with number of 244 (30.9%), *Klebsiella pneumoniae* 134 (17%), *Pseudomonas aeruginosa* 91 (11.5%), *Escherichia coli* 58 (7.3%), and *Enterobacter cloacae* 45 (5.7%).

Of the 1,364 CAP patients, there were 294 (21.5%) MDRO. This was more than the study in the United States that reported there were 5/263 (1.9%) MDRO in CAP.[14] A study in Italy reported the prevalence of MDRO in CAP was 8.1% in Italy (especially MRSA, MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[15] Whereas, a study in Spain reported 22/68 (32%) MDR *Pseudomonas aeruginosa* in CAP.[16]

The five most common MDRO (**Table 3**) were MDR *Acinetobacter baumannii,* MDR *Klebsiella pneumonia,* MDR *Escherichia coli,* MDR *Pseudomonas aeruginosa,* and MDR *Enterobacter cloacae.* Rice,[17] stated that *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter species are highly important because they comprise the largest part of the nosocomial infections and they represent the paradigms of pathogenesis, transmission, and resistance as well. Previous study by Sievert et al,[18] also showed the occurrence of multidrug-resistant gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacter* spp.

Various factors have been shown to predispose patients to MDROs infection including patients' severity of illness, functional disability, advanced dementia, dialysis, diabetes mellitus, renal failure, structural lung disease, and chronic obstructive pulmonary disease (COPD), liver failure or other organ failure and surgical procedures, indwelling devices (urinary catheters and/or feeding tubes), fecal incontinence, previous antibiotic exposure, recent hospitalization, traveling to high prevalence countries and antimicrobial use during travels.[19-21]

Patients with a history of previous hospitalization were considered as CAP in this study. In the previous 2005 ATS guideline, patients who were hospitalized in an acute care hospital for two or more days within 90 days of the infection are considered as HCAP,[7] but in the 2016 ATS guideline, HCAP was included in CAP because patients with HCAP are similar to those with CAP, frequently present from the community and are initially cared for in emergency department.[8] Our study found that infection of MDRO were associated with previous hospitalization (OR=1.737; 95% CI=1.320-2.286), malignancy (OR=2.134; 95% CI=1.455-3.131), cardiovascular disease (OR=1.744; 95% CI=1.174-2.591), and structural lung disease (OR=2.816; 95% CI=1.833-4.327) as presented in **Table 5**. Previous hospitalization in CAP patients should be a concern due to the higher risk for MDRO infection.

The infection of certain MDR pathogens may be associated with certain variables. Huang et al,[22] reported that MDR *Acinetobacter baumannii* infection was associated with sex, age, hospitalization times, history of cancer, HAI, ICU days, mechanical ventilation, indwelling catheters, the combined use of antimicrobial agents before infection, and the use of third-generation cephaloglycin. Mody et al.[23] showed that MDR *Acinetobacter baumannii* caused infection in older adults treated as inpatients in a long term, particularly older adults using invasive devices and/or those with underlying accompanying diseases. Nursing home (NH) residents also bear a number of the risk factors that likely to allow MDR *Acinetobacter baumannii* colonization or infection, including chronic obstructive pulmonary disorder, cardiac and renal failure, diabetes mellitus, dementia, presence of wounds, and use of antibiotics and invasive devices, for example, urinary catheters.

Research by Silva[24] found that malignant underlying disease is the major risk for infection by ESBL-producing *Klebsiella pneumoniae*. However, other identified risks such as urinary and central venous catheter, and other invasive devices, anemia, as well as older age were not related to such infections. Cheng et al,[25] reported that ESBL-producing bacteremic pneumonia (*Escherichia coli* and *Klebsiella pneumoniae* that produces ESBL), often occurred in adults

with comorbidities.

Dantas et al.[26] reported that common independent risk factors for antimicrobial *Pseudomonas aeruginosa* resistance are previous antibiotic use, length of hospitalization being 30 days or longer prior to *Pseudomonas aeruginosa* infection, hemodialysis, tracheostomy, pulmonary source of bacteremia and Intensive Care Unit admission. Functional status, pulmonary comorbidity, nursing home residence, previous hospitalization, and previous antibiotic therapy are factors that have a remarkable relationship with the acquiescence of potentially drug-resistant pathogens in immunocompetent patients inflicted with pneumonia outside the hospital.[27] Two possible factors for the impact of previous hospitalization and nursing home residency on resistant pathogen infection including; first, the impact could be related to exposure to a broad antibiotic coverage in these settings that leads to selection pressure for resistance. Second, the tenacity of MDR pathogens in various wards and transmission among healthcare providers and patients is increasing, and powerful healthcare policies are needed to reduce these pathogens.[28,29]

The limitation of this study was the variables of recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection, and history of attending a hospital and hemodialysis clinic in patients with comorbid of renal failure were not analyzed for risk factors of MDRO infection.

CONCLUSION

The occurrence of MDRO in CAP is high (21.5%). The most common pathogen is *Acinetobacter baumannii.* The crucial factors associated with MDRO in CAP are previous hospitalization, malignancy, cardiovascular disease, and structural lung disease.

CONFLICT OF INTEREST

There is no conflict of interest.

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Factors Associated with Arterial Stiffness in Chronic Hemodialysis Patients in Jakarta: The Role of Hemodialysis Frequency and Pentraxin 3

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ABSTRAK

Latar belakang: *kekakuan arteri merupakan prediktor mortalitas pada pasien hemodialisis, hemodialisis menginduksi inflamasi, ditandai dengan peningkatan intradialisis pada penanda inflamasi pentraxin 3 (PTX3). Kekakuan arteri pada pasien hemodialisis dua kali seminggu di Indonesia lebih rendah daripada yang ditemukan dalam studi pasien tiga kali seminggu. Oleh karena itu, penelitian ini bertujuan untuk mengetahui faktor-faktor yang berhubungan dengan kekakuan arteri, dengan fokus pada peran frekuensi hemodialisis dan PTX3.* ***Metode:*** *studi potong lintang dilakukan di RS. Cipto Mangunkusumo, RS. Fatmawati, dan RS. Medistra pada pasien hemodialisis dua kali dan tiga kali seminggu. Kekakuan arteri diukur dengan kecepatan gelombang nadi karotis-femoralis setelah hemodialisis, dan sampel darah untuk pengujian PTX3 diambil sebelum hemodialisis. Analisis bivariat dan multivariat dilakukan dengan menggunakan uji chi-kuadrat dan regresi logistik.* ***Hasil:*** *dari 122 subjek, 82 menjalani hemodialisis dua kali seminggu. Tidak ada perbedaan dalam kekakuan arteri antara subjek dua kali dan tiga kali seminggu. Dalam analisis bivariat, PTX3, penyakit kardiovaskular, dialisis vintage memiliki nilai p <0,05, sedangkan analisis multivariat berikutnya menunjukkan bahwa PTX3>2,3 ng/ml dikaitkan dengan kekakuan arteri (OR 5,18; 95% IK 1,07-24,91), sebagai serta penyakit kardiovaskular (disesuaikan OR 3,67; 95% IK 1,40-10,55), LDL (disesuaikan OR 3,10; 95% IK 1,04-9,24), dan dialisis vintage (disesuaikan OR 2,72; 95% IK 1,001-7,38).* ***Kesimpulan:*** *kadar PTX3 pradialisis di atas 2,3 ng/ml berhubungan dengan kekakuan arteri. Tidak ada perbedaan kekakuan arteri antara pasien hemodialisis dua kali dan tiga kali seminggu.*

Kata kunci: *kekakuan arteri, kecepatan gelombang nadi, pentraxin 3, frekuensi hemodialisis.*

ABSTRACT

Background: *arterial stiffness is a mortality predictor in hemodialysis patients, hemodialysis induces inflammation, marked by an intradialysis increase in the inflammatory marker pentraxin 3 (PTX3). Arterial stiffness in twice-weekly hemodialysis patients in Indonesia is lower than has been found in studies of thrice-weekly patients. This study therefore aims to determine the factors associated with arterial stiffness, focusing on the role of hemodialysis frequency and PTX3.* ***Methods:*** *a cross-sectional study was conducted at Cipto Mangunkusumo*

Hospital, Fatmawati Hospital, and Medistra Hospital involving patients with twice- and thrice-weekly hemodialysis. Arterial stiffness was measured by carotid-femoral pulse wave velocity after hemodialysis, and blood samples for PTX3 testing were taken before hemodialysis. Bivariate and multivariate analyses were performed using chi-squared tests and logistic regression. ***Results:*** *out of 122 subjects, 82 underwent twice-weekly hemodialysis. There was no difference in arterial stiffness between patients with twice- and thrice-weekly hemodialysis. In bivariate analysis, PTX3, cardiovascular disease, dialysis vintage had p values of <0.05, while the subsequent multivariate analysis showed that PTX3>2.3 ng/ml was associated with arterial stiffness (adjusted OR 5.18; 95% CI 1.07–24.91), as well as cardiovascular disease (adjusted OR 3.67; 95% CI 1.40–10.55), LDL (adjusted OR 3.10; 95% CI 1.04–9.24), and dialysis vintage (adjusted OR 2.72; 95% CI 1.001–7.38).* ***Conclusion:*** *predialysis PTX3 levels above 2.3 ng/ml were associated with arterial stiffness. There was no difference in arterial stiffness between patients with twice- and thrice-weekly hemodialysis.*

Keywords: *arterial stiffness, pulse wave velocity, pentraxin 3, hemodialysis frequency.*

INTRODUCTION

Cardiovascular diseases are the leading cause of death in the chronic hemodialysis population.[1] Previous studies have shown that the increased cardiovascular risk may be due to early vascular structure changes toward a stiffer vasculature, and arterial stiffness is an independent predictor of mortality in hemodialysis patients.[2]

CKD is a proinflammatory condition in which there is an increase in the production of prooxidant molecules, disruption of oxidative product clearance, and antioxidant deficiency. Along with traditional cardiovascular risk factors, inflammation can accelerate arterial stiffness, which is also exacerbated by vascular calcification as a manifestation of bone mineral disorders in CKD.[3] The gold standard for arterial stiffness measurement is pulse wave velocity (PWV) in the carotid-femoral axis,[2] and a PWV value of 10 m/s or greater has been recommended as a suitable cut-off for an increased risk of cardiovascular mortality.[4]

Hemodialysis is a process that cleans various uremic toxins and withdraws excess fluid, but the exposure of blood to an artificial dialyzer membrane during hemodialysis can induce inflammation.[5-8] Pentraxin 3 (PTX3), a marker of inflammation, starts to increase 30 minutes after hemodialysis begins and continues increasing until hemodialysis ends.[9] This prompts the presumption that, if hemodialysis is done more frequently or for longer periods, the patient will have increased risk of inflammation due to more frequent exposure to the dialyzer. PTX3 is closely associated with cardiovascular disease and a mortality predictor in hemodialysis patients,[10,11] but there are to date no published studies regarding PTX3 and arterial stiffness in the hemodialysis population.

At present, most hemodialysis in Indonesia is done twice weekly for a total of 10 hours, whereas the hemodialysis recommendations according to KDOQI are thrice weekly for a total of 12 hours.[12] Sari et al. found that arterial stiffness in twice-weekly hemodialysis patients is lower than has been found in studies done in thrice-weekly hemodialysis patients.[13,14] Inflammation due to hemodialysis has a strong role in the pathophysiology of arterial stiffness, and this study was therefore conducted to assess the association of hemodialysis frequency and PTX3 with arterial stiffness in hemodialysis patients, adjusted for other known risk factors.

METHODS

This was a cross-sectional study conducted in hemodialysis units in Cipto Mangunkusumo National General Hospital, Fatmawati General Hospital, and Medistra Hospital in December 2019. Subjects with a hemodialysis vintage of more than 1 year gave informed consent to participate in the study, which was approved by the local ethical committee. Exclusion criteria were conditions that prevented neck examination, hemodynamic disorders, fluid overload, malignancy, pregnancy, using immunosuppressant drugs, acute infections, and lack of cooperation. This study has been

approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia (Ref. Number KET-1318/UN2.F1/ETIK/PPM.00.02/2019).

Measurement of PWV

Vascular studies were performed with subjects resting in a supine position after the hemodialysis session ended. PWV was measured in the carotid and femoral arteries using a PWV machine (Syphgmocor XCEL, AtCor Medical) in accordance with the manufacturer's recommendations. PWV was automatically calculated by measuring the time for the pulse wave to travel between the carotid and femoral arteries.

Clinical Examination

Clinical parameters, including BMI, gender, age, smoking status, and history of cardiovascular diseases, were collected from medical records. Interdialytic weight gain (IDWG) was operationalized as the mean IDWG over one month.

Malnutrition was assessed with a subjective global assessment, on the basis of which patients' nutritional status was graded as A, B, or C. In this study, grades B and C were combined and considered as malnourished.

Biochemical Analysis

Peripheral blood was collected before hemodialysis on Wednesday or Thursday for thrice-weekly subjects and on Thursday, Friday, or Saturday for twice-weekly subjects. Blood samples were placed in an EDTA tube and centrifuged at 1,000 g (approximately 3,000 rpm) for 15 minutes. The analysis was carried out with the Quantikine® ELISA Human Pentraxin 3/ TSG-14 Immunoassay (R&D systems) reagent in the Prodia laboratory. Measurements were performed using routine laboratory methods for serum parameters such as hemoglobin, creatinine, calcium, phosphate, and low-density lipoprotein. Hyperphosphatemia was defined as serum phosphate above 4.6 mg/dl. Hypercalcemia was defined as serum calcium above 10 mg/dl.

Statistical Analysis

The data was processed using IBM SPSS 25. Numerical data with normal distributions is expressed as mean (SD), while data with abnormal distributions is expressed as median (min–max). Bivariate analysis was conducted with chi-squared tests, and multivariate analysis was performed with logistic regression.

RESULTS

Of the 122 subjects, 80 were twice-weekly hemodialysis patients. The mean age was 52.7 years old, and 54.9% were male. Diabetes was found in 32.8% of subjects, hypertension in 82.8%, and arterial stiffness in 21.3%. No

Table 1. Baseline characteristics of the study population.

Parameters	HD twice weekly (n=82)	HD thrice weekly (n=40)	Total (n=122)
Gender–male, n (%)	45 (54.8)	22 (55.0)	67 (54.9)
Age, years, mean (SD)	49.79 (14.58)	58.73 (14.97)	52.72 (15.24)
Dialysis vintage, months, median (range)	72 (12–236)	32.5 (13–119)	54 (13–236)
Diabetes mellitus, n (%)	22 (26.8)	20 (50)	40 (32.8)
Hypertension, n (%)	71 (86.5)	30 (75)	101 (82.8)
Cardiovascular disease, n (%)	18 (21.9)	12 (30)	30 (24.6)
LDL cholesterol, mg/dl, median (range)	101 (25–189)	110 (41–219)	105 (25–219)
Phosphate, mg/dl, median (range)	5.55 (1.2–10.8)	4.55 (2.2–9.3)	5.25 (1.0–10.8)
Hyperphosphatemia, n (%)	61 (74.4)	17 (42.5)	78 (63.9)
Hypercalcemia, n (%)	9 (10.9)	1 (2.5)	10 (8.2)
Hemoglobin, g/dl, mean (SD)	9.74 (1.60)	10.05 (1.63)	9.84 (1.60)
Malnutrition, n (%)	4 (4.8)	8 (20)	12 (9.8)
Albumin, g/dl, mean (SD)	3.98 (0.35)	3.87 (0.41)	3.95 (0.37)
IDWG, kg, mean (SD)	3.30 (0.90)	1.78 (0.80)	2.80 (1.11)
IDWG > 5%, n (%)	55 (67.1)	1(2.5)	56 (45.9)
PWV, m/s, mean (SD)	8.72 (2.04)	8.79 (1.71)	8.75 (1.93)
PTX3, ng/ml, mean (SD)	1.14 (0.83)	1.05 (0.61)	0.93 (0.05–4.65)
PTX3 > 2.3 ng/ml, n (%)	6 (7.3)	3 (7.5)	9 (7.4)

Table 2. Bivariate analysis between dependent variables and arterial stiffness.

Variables		Arterial stiffness		p	OR
		PWV ≥10 m/s n = 26 n (%)	PWV<10 m/s n = 96 n (%)		
HD frequency	Twice weekly	19 (23.2)	63 (76.8)	0.473	1.32 (0.60–2.8)
	Thrice weekly	7 (17.5)	33 (82.5)		
PTX3	>2.3 ng/ml	5 (55.6)	4 (44.4)	0.021	2.98 (1.48–6.02)
	≤2.3 ng/ml	21 (18.6)	92 (81.4)		
Age	>60 years	8 (20.5)	31 (79.5)	0.883	0.94 (0.45–1.98)
	≤60 years	18 (21.7)	65 (78.3)		
Diabetes mellitus	Yes	10 (23.8)	32 (76.2)	0.625	1.19 (0.59–2.38)
	No	16 (20.0)	64 (80.0)		
Hypertension	Yes	22 (21.8)	79 (78.2)	1.0	1.14 (0.44–2.97)
	No	4 (19.0)	17 (81.0)		
LDL cholesterol	>100 mg/dl	20 (26.3)	56 (73.7)	0.11	2.01 (0.87–4.65)
	≤100 mg/dl	6 (13.0)	40 (87.0)		
Malnutrition	Yes	3 (25.0)	9 (75.0)	0.718	1.19 (0.42–3.40)
	No	23 (20.9)	87 (79.1)		
Cardiovascular disease	Yes	12 (40.0)	18 (60.0)	0.004	2.62 (1.37–5.0)
	No	14 (15.2)	78 (84.8)		
Dialysis vintage	>54 months	18 (28.6)	45 (71.4)	0.043	2.1 (0.99–4.47)
	≤54 months	8 (13.6)	51 (86.4)		
Serum calcium	Hypercalcemia	2 (20.0)	8 (80.0)	1.0	0.93 (0.25–3.38)
	Not hypercalcemia	24 (21.4)	88(78.6)		
Serum phosphate	Hyperphosphatemia	18 (23.1)	60 (76.9)	0.526	1.27 (0.60–2.67)
	Not hyperphosphatemia	8 (18.2)	36 (81.8)		
IDWG	>5% dry weight	12 (21.4)	44 (78.6)	0.97	1.01 (0.51–2.00)
	≤5% dry weight	14 (21.2)	52 (78.8)		

Table 3. Multivariate analysis of arterial stiffness and Pentraxin 3, cardiovascular disease, dialysis vintage, and LDL cholesterol.

Variables	Adjusted OR	95% CI	p value
PTX3	5.18	1.07–24.91	0.04
Cardiovascular disease	3.67	1.40–10.55	0.009
Dialysis vintage	2.72	1.001–7.38	0.05
LDL cholesterol	3.10	1.04–9.24	0.042

subjects were smoking at the time of the study. (**Table 1**) Compared to the thrice-weekly hemodialysis subjects, the twice-weekly subjects were younger and had longer dialysis vintage, lower LDL cholesterol, and higher IDWG. There were no differences in PWV and PTX3 between patients with twice- and thrice-weekly hemodialysis.

In the bivariate analysis (**Table 2**), PTX3, cardiovascular disease, and dialysis vintage were found to be associated with arterial stiffness. The multivariate analysis (**Table 3**) showed the same, in addition to an association with LDL cholesterol.

DISCUSSION

Arterial stiffness was found in 21.3% of subjects. This proportion is lower than found by Sari et al.[13], at 30%, and by Utescu et al.[14], at 43%; the mean PWV in this study was also lower than found by Sari et al.[13] in twice-daily hemodialysis patients, at 9.0 (SD 2.2) m/s. The mean PWV in thrice-weekly subjects was 8.79 (SD 1.71) m/s, lower than found in thrice-weekly subjects by Utescu et al. (13.1 (SD 3.7) m/s), lower than in a study conducted by Wang et al. in stage 5 non-dialysis CKD subjects (11.6 (SD 3.3) m/s), and lower than in a study conducted by Krishnasamy et al. in stage 4 and 5 CKD subjects (9.7 m/s [7.6–11.7]).[14-16] Previous studies have

shown that arterial stiffness in hemodialysis patients is higher than in the normal population. This is due to traditional cardiovascular risk factors; vascular calcification, which is a manifestation of bone mineral disorders in CKD; and inflammations that accelerate changes in the blood vessel structure. The low PWV and lower proportion of arterial stiffness in this study need to be compared with the average PWV in the healthy population in Indonesia, but there have so far been no studies of arterial stiffness in this population.

The proportions of arterial stiffness in patients with twice- and thrice-weekly hemodialysis were not statistically different. The similarity in arterial stiffness between the two groups may be caused by differences in dialysis vintage. Patients with twice-weekly hemodialysis had higher dialysis vintage—almost twice that of thrice-weekly subjects (72 months [12–236] vs. 32.5 months [13–119]; p = 0.000)—so the twice-weekly subjects experienced longer inflammatory exposure due to hemodialysis.

PTX3 is an inflammation marker that increases during hemodialysis; the median PTX3 in this study was 0.93 ng/ml (0.05–4.65), lower than found by Suliman et al. (10.6 ng/ml [2.4–75.1]), El Sebai et al. (2.3 ng/ml (0.9–33)), and Oglio et al. (2.4 (SD 0.6) ng/ml).[9,17,18] PTX3 in this study was taken predialysis, similar to the other studies, so the median value of PTX3 may have been lower in this study due to differences in the subject selection criteria; for example, El Sebai et al. did not exclude subjects with malignancies. In the bivariate and multivariate analysis, PTX3 was found to be associated with arterial stiffness, which suggests that inflammation is an independent factor related to arterial stiffness. This study is the first to find an association between PTX3 and arterial stiffness in hemodialysis patients.

The proportions of PTX3 >2.3 ng/ml in patients with twice- and thrice-weekly hemodialysis were similar, despite differences in the characteristics of the two groups. The increasing value of PTX3 might have returned to baseline value intradialysis, similar to as Sjöberg et al.[19], who found in a sub-analysis of seven hemodialysis patients that baseline predialysis PTX3 values in three consecutive hemodialysis sessions with intervals of 1 or 2 days did not differ.

The proportion of arterial stiffness was higher in subjects with cardiovascular disease (40% vs 15.2%; p = 0.004). This was in line with previous studies, which found that PWV is an independent predictor of cardiovascular mortality.[20-23] PTX3 is an acute phase reactant released by neutrophil granules in response to a stimulus that triggers inflammation,[24] and its expression in macrophages and endothelial cells has been found to be stronger in mice with advanced atherosclerotic lesions than those without. Oglio et al.[9] found an increase in intracellular PTX3 expression in neutrophils at the end of hemodialysis, and intracellular PTX3 concentration is correlated with endothelial dysfunction, which contributes to the pathophysiology of cardiovascular disease.

We found dialysis vintage to be one of the determinants of arterial stiffness, as the proportion of arterial stiffness was higher in subjects with longer dialysis vintage. This is in line with a cohort study by Goldsmith et al.[25], which found that the proportion of vascular calcification increased from 49% at the onset of hemodialysis to 92% after hemodialysis for 9.7 years; dialysis vintage was also a determining factor for the severity of vascular calcification, which is one of the contributing factors for arterial stiffness.

Arterial stiffness was also found to be associated to LDL cholesterol in the multivariate analysis. One of the mechanisms that may explain the relationship between LDL and arterial stiffness is the formation of atherosclerotic plaque. Dyslipidemia is closely related to oxidative stress and inflammation, and, in hyperlipidemic conditions, lipoprotein is more susceptible to oxidation, and the oxidized form is more atherogenic. Oxidized LDL will therefore enter arterial wall macrophages faster.[26]

The proportion of subjects with arterial stiffness was not different between subjects aged 60 years and older, and those younger than 60 years. Previous studies suggested age as risk factor for arterial stiffness, but this study found no association between age and arterial stiffness. In CKD patients, arterial stiffness occurs at

an earlier age, which is called early vascular aging.[27] The lack of difference in arterial stiffness between the two age groups was probably due to differences in dialysis vintage; the dialysis vintage of subjects under 60 years was almost twice that of those older than 60 (83.2 (SD 53.3) months vs 46.8 (SD 32.1) months; $p < 0.001$). Therefore, younger subjects experienced longer exposure to inflammation due to hemodialysis. The effect of longer dialysis vintage in arterial stiffness probably outweighed the effect of older age.

The proportion of arterial stiffness did not differ between subjects with IDWG above 5% of dry body weight and those below. The similarity in arterial stiffness in both IDWG groups caused by PWV in this study was examined post-dialysis, thereby eliminating the overhydration factor.

We found no association between diabetes mellitus, hypertension, serum calcium, or phosphate and arterial stiffness, despite all of them playing important roles in the pathology of arterial stiffness. This is one of our study limitations, in that we did not consider the duration, severity, and long-term control of diabetes and hypertension. Our study only involved a one-time examination of serum calcium and phosphate, so it might not reflect their long-term control.

This study has other limitations. It was a cross-sectional study, so we were not able to assess long-term metabolic control. We were also unable to achieve similar proportions of patients with thrice- and twice-weekly hemodialysis with similar dialysis vintages, and we could not achieve a balanced proportion of patients with thrice- and twice-weekly hemodialysis overall, even though the number of subjects had already met the minimum sample size. We also did not examine post-dialysis PTX3, so we were unable to see the role of hemodialysis in increasing the inflammatory response. All variables that had a significant association with arterial stiffness in the multivariate analysis had wide confidence intervals; this could be narrowed if the study sample were larger.

CONCLUSION

In summary, predialysis PTX3 above 2.3 ng/ml was associated with arterial stiffness, as was cardiovascular disease, dialysis vintage, and LDL cholesterol level. This study found no association between hemodialysis frequency and arterial stiffness.

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A Survival Analysis of Successful and Poor Treatment Outcome Among Patients with Drug-Resistant Tuberculosis and the Associated Factors: A Retrospective Cohort Study

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ABSTRAK

Latar belakang: *Tuberkulosis dan resistensinya merupakan masalah kesehatan global yang utama di dunia. Peningkatan insiden dan kematian tuberkulosis di Indonesia masih menjadi masalah kesehatan masyarakat yang besar khususnya di Provinsi DKI Jakarta. Tidak ada penelitian yang dipublikasikan yang berfokus pada penilaian hasil pengobatan resistensi tuberkulosis baik dalam keberhasilan maupun kematian. Oleh karena itu, penelitian ini bertujuan untuk menilai hasil kesembuhan dan kematian serta faktor-faktor penentu yang mungkin mempengaruhi resistensi obat TB di Provinsi Kota Jakarta antara tahun 2010 dan 2015.* ***Metode:*** *penelitian ini menganalisis register elektronik tuberkulosis nasional (e-TB Manager) Provinsi Jakarta pada tahun 2010 hingga 2015. Semua pasien dewasa yang tinggal di provinsi Jakarta dan didiagnosis dengan TB-MDR (multidrug-resistant tuberculosis) dan TB resistan obat ekstensif (XDR-TB) memenuhi syarat untuk penelitian. Kurva kelangsungan hidup Kaplan Meier digunakan, bersama dengan uji log-rank dan uji Chi-Square (X2) untuk analisis deskriptif. Analisis regresi Cox dijalankan untuk menentukan faktor risiko potensial. Beberapa faktor risiko dianalisis dalam penelitian ini, termasuk usia, jenis kelamin, tempat tinggal, status HIV, status resistensi, dan riwayat pengobatan sebelumnya.* ***Hasil:*** *secara keseluruhan, 553 sampel yang memenuhi syarat dianalisis dalam penelitian ini. Resistensi obat tuberkulosis meningkat secara bertahap selama tahun 2010 hingga 2015, dimana masing-masing 248 dan 67 pasien yang termasuk dalam penelitian ini sembuh dan meninggal. Ada perbedaan tingkat kelangsungan hidup dengan pengobatan yang berhasil (sembuh) antara pasien yang didiagnosis dengan MDR-TB dan XDR-TB. Perawatan yang buruk (kematian) di antara pasien diprediksi oleh usia lebih dari 60 tahun (HR 3,48; 95% CI 1,48 – 8,38, p-value = 0,004).* ***Kesimpulan:*** *ada perbedaan angka kelangsungan hidup antara keberhasilan pengobatan (sembuh) dan pengobatan yang buruk (kematian) selama enam tahun pengamatan. Usia pasien adalah prediktor tunggal dalam kelangsungan hidup kematian. Sedangkan status HIV dan status resistensi merupakan prediktor kelangsungan hidup orang yang sembuh.*

Kata kunci**:** *MDR, XDR, Tuberkulosis, resistensi, analisis kesintasan.*

ABSTRACT

Background: *Tuberculosis and its resistance are a major global health problem in the world. The increased incidence and mortality of tuberculosis in Indonesia remain a big public health issue especially in Jakarta Province. No published studies have focused on assessing the outcome treatment of tuberculosis resistance both in success and death. We aimed this study to assess the survival of cured and death outcomes as well as the determinant factors which might influence drugs resistant tuberculosis in Jakarta between 2010 and 2015.* ***Methods:*** *this study analyzed the national electronic tuberculosis register (e-TB Manager) of Jakarta province in 2010 to 2015. All adult patients who lived in Jakarta province and were diagnosed with multidrug-resistant tuberculosis (MDR-TB)*

and extensively drug-resistant tuberculosis (XDR-TB) were eligible for the study. Kaplan Meier survival curve was used, together with log-rank test and Chi-Square (X^2) test for descriptive analysis. Cox regression analysis helped determine the potential risk factors. Several risk factors were analyzed in this study, including age, gender, residency, HIV status, resistance status, and history of previous treatment. ***Results:*** *we analyzed 553 samples in this study. The drug-resistant tuberculosis cases increased gradually from 2010 to 2015. Of all cases, 248 and 67 patients were cured and death, respectively. There was a difference in survival rate between patients diagnosed with MDR-TB and XDR-TB with successful treatment. Poor treatment outcome (death) among patients was predicted by age greater than 60 years old (HR 3.48; 95% CI 1.48 – 8.38, p-value = 0.004).* ***Conclusion:*** *there was a difference survival rates between success treatment (cured) and poor treatment outcome (death) during six years of observation. Age of patients is a single-predictor in survival of death. While, HIV status and resistance status were predictors in survival of cured.*

Keywords**:** *MDR, XDR, Tuberculosis, resistance, survival analysis.*

INTRODUCTION

Tuberculosis (TB) remains one of the major global health challenges in the world. In 2018, it was estimated that tuberculosis mortality rates were 11 per 100,000 among HIV-negative people and 0.31 per 100,000 among HIV-positive people.[1] World Health Organization (WHO) also reported that 43% and 83% of bacteriologically confirmed TB cases tested for Rifampicin resistance as new cases and previously treated cases in 2018, respectively[1]. Furthermore, there were 5,584 multidrug-resistant tuberculosis (MDR/RR-TB) cases confirmed by laboratory and 4,566 cases of them started on treatment[1]. On the other hand, 122 cases of extensively drug-resistant tuberculosis (XDR-TB) were detected and 100 of them started on treatment. The treatment success rate for new cases of MDR-TB/RR-TB and XDR–TB reached 65% and 37%, respectively.[1]

Indonesia is one of ten countries that account for 75% of the global gap between treatment enrolments and the estimated number of new cases of MDR/RR-TB in 2018. Based on Indonesian national health survey in 2018, the prevalence of lung tuberculosis reached 42%. Treatment outcomes of tuberculosis in Indonesia for new, relapsed (previously treated, excluding relapsed in 2016), MDR-TB (2015 cohort), and XDR-TB (2015 cohort) were reported as 86%, 71%, 47%, and 28%, respectively.[1] Jakarta had the highest number of tuberculosis cases in Indonesia with 37,114 cases in 2018.[2] The Jakarta Province Health Office [3] reported that new cases of tuberculosis in 2017 was 12,880 which around 10,709 received anti-tuberculosis treatment.[4] From those who had anti-tuberculosis treatment, forty-eight percent completed the treatment, and the success rate was 77%, while 465 deaths (four cases per 100,000 population) were attributed to tuberculosis in Jakarta.[4] This circumstance might occur due to the Jakarta's population density in 2018 which was 17,200/km^2 (the WHO standard of population density is 9,500/km^2).[5] Studies pointed out that population density are the key factor that influences the transmission of tuberculosis.

Treatment of resistant tuberculosis requires a long duration and high cost, but previous studies showed highly successful outcomes in some countries.[6-8.] Several factors were significantly associated with the treatment outcomes of resistant tuberculosis. These included patient characteristics, such as age, sex, socio-economic status, patient compliance during treatment, nutritional status, smoking, alcohol consumption, comorbidities, anti-tuberculosis treatment side effects, and additional nutrients (vitamin D, vitamin C, Potassium and others) during treatment.[9-17]

Although several studies showed that individual treatment regimens among patients with MDR tuberculosis could achieve profitable outcomes in more than 60% of cases,[6-8] only few studies assessed the risk factors of outcome treatment in both positive and negative result among TB patient through retrospective data in Indonesia. Due to the large population,

high density, and multicultural population of Indonesia, the results of previous studies cannot be simply applied to Indonesian condition. Therefore, we aimed to assess success treatment (cured) and poor treatment outcome (death) and factor associated of resistant tuberculosis in patients in Jakarta City province between 2010 and 2015.

METHODS

An observational retrospective cohort study was conducted in Jakarta, which consists of five cities and one district. The observation was documented from 2010 to 2015 in all areas, including South Jakarta, West Jakarta, North Jakarta, East Jakarta, Central Jakarta and Kepulauan Seribu. The observation started from diagnosis after sputum culture result and ended when a final event occurred (cured or deceased) or after 30 months of treatment. The factors that observed including characteristic demography, resistance status, tuberculosis treatment regimen, and duration of tuberculosis treatment. The outcomes were cured and deceased as success or failure of treatment during the observation period.

Data Sources and Measurement

This study was the continuation of our previous study "Determinant factors of drop out among multi drugs resistance Tuberculosis (MDR TB) patients at Jakarta Province from 2011 to 2015", published in the Indonesian Journal of Tropical and Infectious Disease in September 2018. The national electronic tuberculosis register (e-TB Manager) of Jakarta province in 2010 to 2015 was used as the data source. These data are the national tuberculosis surveillance system in Indonesia and consist of demographic and clinical information along with initial assessment and follow-up during antimicrobial treatment using sputum culture test and GeneXpert as the rapid test.

Participants

All adult patients (> 18 years old) living in Jakarta province and were diagnosed with drug-resistant tuberculosis between 2010 and 2015 were eligible for the study. Only patients with MDR-TB and XDR-TB were included. Those who were diagnosed with mono-resistance and poly-resistance were excluded. All patients were evaluated from diagnosis to the end of treatment (cured or deceased) started from 2010 to 2015. Totally, there were 630 eligible patients who were diagnosed with MDR-TB and XDR-TB living in DKI Jakarta and received tuberculosis treatment.

Variables

Variables were observed, including sex, age, and residency, HIV status, drug-resistance, and history of previous treatment. The age groups consisted of the following five categories: less than 30 years old, 30 to 39 years old, 40 to 49 years old, 50 to 59 years old, and greater than 60 years old. MDR-TB was defined as tuberculosis resistance to at least isoniazid and rifampicin with or without one of the first-line drugs (streptomycin), and XDR-TB was defined as MDR-TB with additional drug resistance to at least one of the injectable second-line drugs (kanamycin, amikacin, and ofloxacin).

Previous treatment refers to a patient history of any previous tuberculosis treatments before starting the current treatment. Incomplete treatment consists of new patients (received tuberculosis treatment for less than two months/ less than 28 doses or never), default treatment (stopped treatment before completion of treatment), and lost to follow-up after at least two months of treatment. Complete treatment consists of failed treatment in first-line or second-line (conversion test after treatment still positive) and relapsed patients (patients who were already cured who returned with resistant tuberculosis infection). The unknown category includes patients without a clear history of previous treatment.

The outcomes of this study were successful treatment (cured) and poor treatment outcome (death). Patients with a negative conversion test result between 0 and 30 months of treatment are considered cured or having had successful treatment. The conversion test used monthly sputum culture. Poor treatment outcome (death) refers to patient death during the treatment and observation periods (30 months).

Statistical Methods

The time variable is time to cure or death measured from admission to date of an event and coded as one (cure or death). Data were transferred to SPSS version 20.0 from Excel version 2017. The variables were then cleaned and coded, and the presence of missing values and influential outliers was checked. Kaplan Meier survival curve was used, together with log-rank test and Chi-Square (X^2) test, for descriptive analysis. Goodness-of-Fit test was used for the presence of different risks in the incidence of cured and deceased among the groups during treatment/ observation. The results of Goodness-of-Fit test indicated that Cox regression proportional hazard analysis could be applied for the survival of poor treatment outcome (death), while successful treatment used an extended Cox regression analysis. The incidence of cure and death with respect to person-time at risk was calculated. The association between variables was summarized by using adjusted hazard ratio, p-value <0.05, and statistical significance tested at 95% confidence interval (CI).

Ethical Clearance

The study used the existing routine information of MDR-TB and XDR-TB treatment that already had permission from the DKI Jakarta Health Office, letter of permission number 1713/ SDK/XI/2017. There was no direct contact with the patients, and informed consent was not obtained from the patients. However, ethical approval was obtained from the previous study that was provided by the Ethical Committee of Public Health Faculty, Universitas Indonesia, number 08/UN2.F10/PPM.00.02/2018.

RESULTS

A total of 553 of 630 eligible patients with a diagnosis of MDR-TB or XDR-TB were analyzed, giving a participation rate of 88% (**Figure 1**). Sixty and 17 patients were diagnosed with mono-resistance and poly-resistance, respectively. **Table 1** shows that about 60% of the patients were men, of which 44% were cured and 10% died during and/or after treatment. The rate of tuberculosis resistance in patients with a history of complete treatment, including failed and relapsed, was 78%. All patients showed resistance to isoniazid and rifampicin, and more than 50% had resistance to streptomycin. Only 1% of the patients were diagnosed as HIV-positive, while the others were HIV-negative (43%) or had unknown status (56%).

The percentage of tuberculosis resistance appears to increase from 81 cases in 2010 to 116 cases in 2015. The following are the six outcomes of tuberculosis resistance treatment between 2010 and 2015: cured after treatment, stopped before completion of treatment, no progress in result of conversion test during and/or after completion of treatment (failed), completion of treatment but no information available related to conversion test, and lost to follow-up (**Table 2**). In this study, the focus was on successful treatment (cured) and poor treatment outcome (death) only. There was a fluctuation in the number of events of cured and deceased during the six years. Overall, survival of cured and death reached 58% and 84%, respectively. While, The median survival time of patients previously treated between 2010 and 2015 were significantly differences of survival of cured and death (**Figure 2** and **3**).

There was a slight difference between treatment for less than 20 months and treatment for greater than 20 months from 2010 to 2015. It was also shown that treatment for greater than 20 months was more likely to be not successful than treatment for less than 20 months. Other variables that can predict survival by successful treatment were resistance status after 20 months of treatment (HR 0.33, 95% CI 0.13 – 0.81), HIV status between zero and before 20 months (HR 0.55, 95% CI 0.39 – 0.78), sex (HR 1.16, 95% CI 1.01 – 1.33) and age during treatment (HR 0.89, 95% CI -.79 – 0.99) (**Table 3**).

Table 4 shows that age greater than 60 years significantly predicted tuberculosis mortality (HR 3.48; 95% CI 1.48 – 8.38 P-value = 0.004), while the area of treatment, history of previous treatment, resistance status, and HIV status were not proven statistically as predictors of tuberculosis mortality.

Table 1. Characteristic demography of MDR-TB and XDR-TB.

Variables	Successful Treatment (Cured)	Poor Treatment Outcome (Death)	Other Outcomes*	Total (n=553)
Sex				
- Male	148 (44.3)	35 (10.5)	151 (45.2)	334 (60.4)
- Female	84 (38.4)	32 (14.6)	103 (47.0)	219 (39.6)
Age (years)				
- < 30	72 (52.6)	12 (8.8)	53 (38.7)	137 (24.8)
- 30 – 39	53 (37.6)	23 (16.3)	65 (46.1)	141 (25.5)
- 40 – 49	60 (42.0)	9 (6.3)	74 (51.2)	143 (25.9)
- 50 – 59	38 (41.3)	12 (13.0)	42 (45.7)	92 (16.6)
- > 60	9 (22.5)	11 (27.5)	20 (50.0)	40 (7.2)
Residency (City/District)				
- South Jakarta	26 (33.8)	9 (11.7)	42 (54.5)	77 (13.9)
- West Jakarta	30 (39.0)	8 (10.4)	39 (50.6)	77 (13.9)
- North Jakarta	23 (30.3)	8 (10.4)	45 (59.2)	76 (13.7)
- East Jakarta	91 (46.0)	17 (8.6)	90 (45.5)	198 (35.8)
- Central Jakarta	29 (46.8)	11 (17.7)	22 (35.5)	62 (11.2)
- Kepulauan Seribu	33 (52.4)	14 (22.2)	16 (25.4)	63 (11.4)
Previous treatment				
- Incomplete	31 (42.5)	6 (8.2)	36 (49.3)	73 (13.2)
- Complete	187 (43.0)	52 (12.0)	196 (45.1)	435 (78.7)
- Unknown	14 (31.1)	9 (20.0)	22 (48.9)	45 (8.1)
Resistance Status				
- MDR-TB	216 (45.2)	55 (11.5)	207 (43.3)	478 (86.4)
- XDR-TB	16 (21.3)	12 (16.0)	47 (62.7)	75 (13.6)
Drug Resistance				
- Isoniazid	232 (42.0)	67 (12.1)	254 (45.9)	553 (100)
- Rifampicin	232 (42.0)	67 (12.1)	254 (45.9)	553 (100)
- Streptomycin	127 (42.6)	43 (14.4)	128 (43.0)	298 (53.9)
- Kanamycin	2 (9.1)	5 (22.7)	15 (68.2)	22 (4.0)
- Amikacin	2 (11.1)	4 (22.2)	12 (66.7)	18 (3.3)
- Ofloxacin	14 (21.2)	10 (15.2)	42 (63.6)	66 (11.9)
HIV Status				
- Negative	79 (33.5)	24 (10.2)	133 (56.4)	236 (42.7)
- Positive	2 (33.4)	2 (33.4)	2 (33.4)	6 (1.1)
- Unknown	151 (48.6)	41 (13.2)	119 (38.3)	311 (56.2)

**Default, failed, and loss to follow-up.*

Table 2. Percentage of the outcome of treatment of MDR-TB and XDR-TB.

Outcome	Frequency	Percent
Cured	248	44.8
Default	156	28.2
Failed	31	5.6
Death	67	12.1
Complete treatment	11	2.0
Loss to follow-up	40	7.3
Total	553	100.0

DISCUSSION

Overall, the survival of successful treatment (cured) and poor treatment outcome (death) were 58% and 84%, respectively. The resistance status after 20 months of treatment, HIV status before 20 months of treatment, sex, and age during treatment were the predictor variables for the survival of successful treatment (cured). While, having elderly patient (>60 years old) was the only predictor variable of poor treatment outcome (death).

The presence of MDR-TB and XDR-TB are predictive factors related to successful treatment. A previous study in Tehran, Iran showed similar results with success rates for treatment of MDR-TB and XDR-TB being different (76.5% and 41.7%, respectively).[18] A study in Hunan, China also had similar results, with MDR-TB having a higher percentage of successful treatment than XDR-TB (38% and 30%, respectively).[19] Conversely, Balabanove et al.[20] did not suggest significant difference in survival of patients with

Table 3. Prediction of successful treatment (cured) among resistant Tuberculosis (Extended Cox Regression analysis).

Covariate	HR (95% CI)	p-value
Sex	1.16 (1.01 – 1.33)	**0.03***
Age (years)	0.89 (0.79 – 0.99)	**0.03***
Area		
- < 20 (months)	1.07 (0.93 – 1.23)	0.53
- ≥ 20 (months)	0.96 (0.85 – 1.10)	0.35
Previous treatment		
- < 20 months	0.85 (0.56 – 1.27)	0.42
- ≥ 20 months	0.72 (0.49 – 1.05)	0.09
Resistance status		
- < 20 months	0.61 (0.31 – 1.18)	0.14
- ≥ 20 months	0.33 (0.13 – 0.81)	**0.01***
HIV status		
- < 20 months	0.55 (0.39 – 0.78)	**0.001***
- ≥ 20 months	1.01 (0.72 – 1.40)	0.98

** p-value < 0.05*

Table 4. Prediction of poor treatment outcome (death) among resistant tuberculosis patients (Cox Regression analysis).

Covariate	HR (95% CI)	p-value
Sex (ref: male)	1.50 (0.92 – 2.54)	0.09
Age (years) (ref: <30)		
- 30 – 39	1.71 (0.83 – 3.52)	0.14
- 40 – 49	0.64 (0.64 – 0.27)	0.32
- 50 – 59	1.56 (1.56 – 0.69)	0.29
- > 60	3.48 (1.48 – 8.38)	**0.004***
Area (ref: South)		
- West Jakarta	0.81 (0.31 – 2.13)	0.68
- North Jakarta	0.94 (0.35 – 2.48)	0.89
- East Jakarta	0.82 (0.36 – 1.88)	0.64
- Central Jakarta	1.65 (0.66 – 4.13)	0.28
- Kepulauan Seribu	1.94 (0.69 – 5.39)	0.20
Complete	1.47 (0.62 – 3.46)	0.38
Unknown	2.45 (0.81 – 7.39)	0.11
Resistance status (ref: MDR-TB)	1.25 (0.65 – 2.45)	0.49
Positive	3.20 (0.69 – 14.93)	0.14
Unknown	2.00 (0.89 – 4.48)	0.09

** p-value < 0.05*

MDR-TB and XDR-TB during treatment (HR = 1.29; 95% CI 0.91 – 1.81, p-value = 0.15). The obvious explanation is the fact of many patients in this study were 'MDRTB plus' with resistance to many other SLD, which made less difference between MDR and XDRTB.

Our analysis also revealed that gender is one of predictor variable for successful treatment (cured), which female was more likely to had experience of successful treatment (cured) than male. This is in line with a previous study from Ethiopia, which found that male MDR-TB patient had tendency to have longer recovery time compared to female. It was hypothesized that male patient was linked to higher tendencies toward alcohol and drug abuse and interruption of their medication. [21] In regards to interruption of medication, a study assessed the influencing factors of non-attendance of health facility for tuberculosis clinical evaluation among household contact. This study found that males were less likely to visit public health facility for Tuberculosis screening compared to women due to the purporting that men visiting clinics are not masculine.[22] Apart from that, Chida et al claimed that gender was not a risk factor for default treatment, because both men and women have similar condition related to economic burden, which affect to their tuberculosis treatment. [23]

There is a difference in survival of successful treatment (cured) among patients with positive, negative, and unknown HIV status. This study showed that HIV diagnosis as a co-infection predicted survival due to successful treatment. Patients diagnosed as HIV-positive and/or unknown status has a higher risk of being non-survivors (unsuccessful treatment) than patients who are HIV-negative.[20,24,25] Girum et al.[25] showed that HIV-positive patients had 3 times higher mortality risk compared with HIV-negative patients. This may be cause HIV status is known as an aggravating comorbidity in tuberculosis patients, and it can influence the treatment outcome [26,27] A previous study in a rural area of South Africa also found that 52 of 53 HIV-positive patients with XDR-TB died, with a median survival of 16 days from the time of diagnosis.[28]

Poor treatment outcome (death) among patients was predicted by age greater than 60 years old (HR 3.48; 95% CI 3.47 – 1.48, p-value = 0.004). Previous studies showed a similar result with patients aged 55 years and older having an almost eight times higher risk of death than patients aged 15 to 34 years.[15,20] Other study suggested age as one of independent predictors of mortality during tuberculosis treatment.[29] A possible explanation is that the elderly population was more likely to have adverse experience of drug reactions to tuberculosis treatment, which may affect treatment outcome.[23] Other than that, age related factors also have impact on poor outcome among elderly people such as multi-

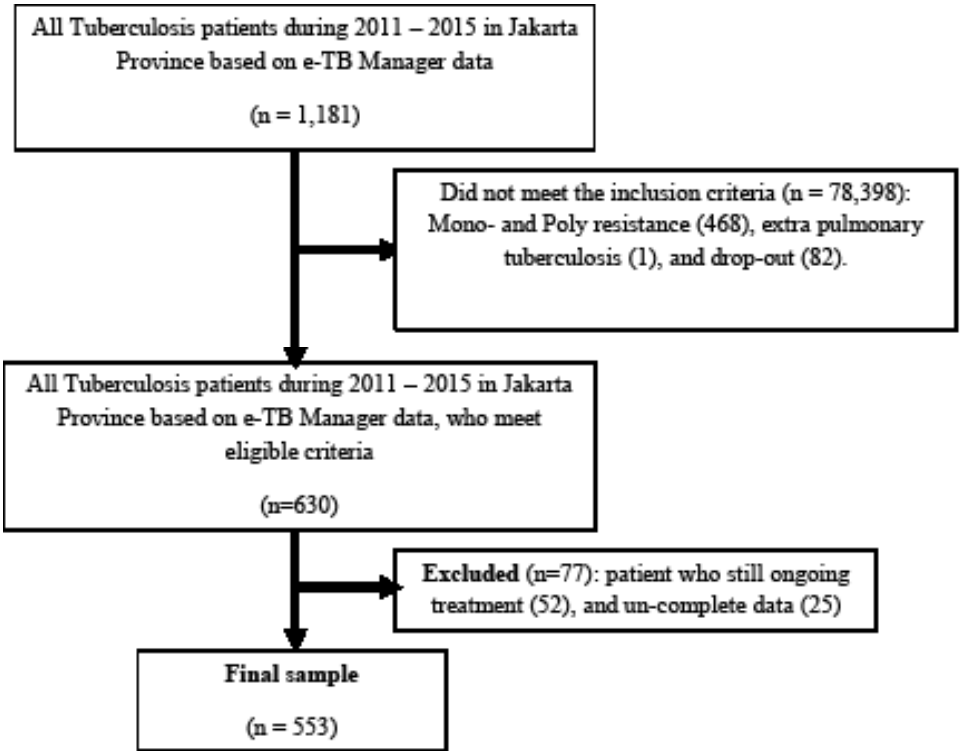

Figure 1. Flow chart of participant selection for the study.

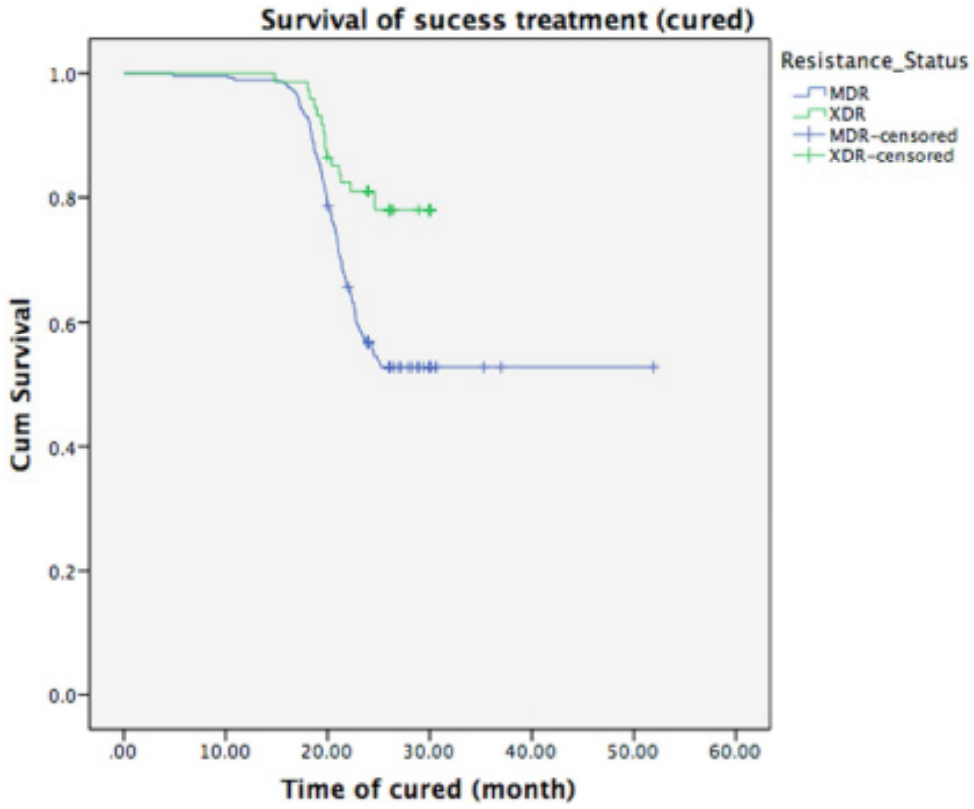

Figure 2. Kaplan-Meier estimates of survival of success treatment or cured among resistant Tuberculosis.

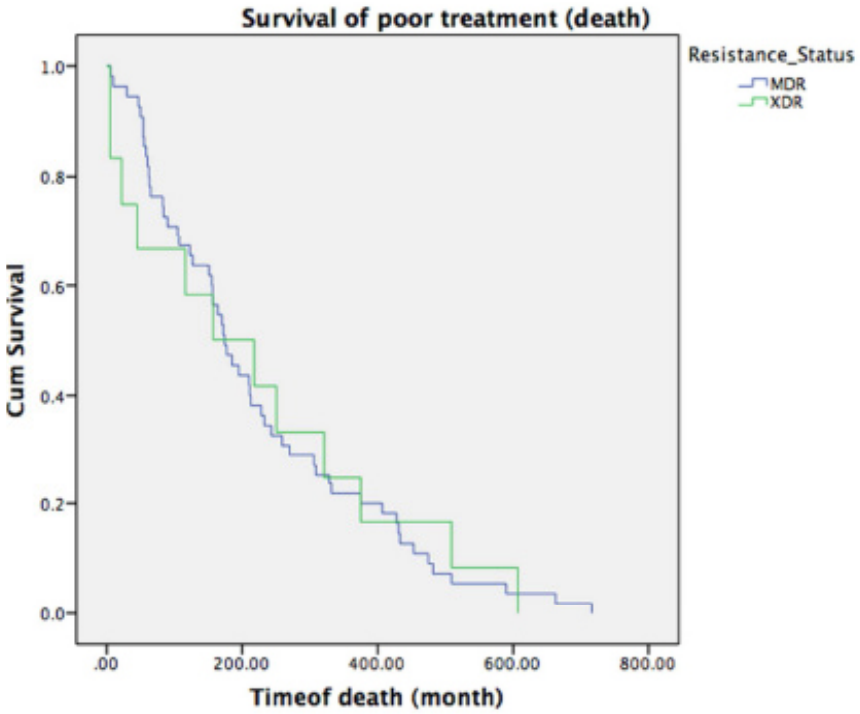

Figure 3. Kaplan-Meier estimates of survival of poor treatment (death) among resistant Tuberculosis.

pathology, cognitive impairment, and economic status. [30]

Some factors could not be assessed due to data limitations. First, this retrospective cohort study did not consider variability over time among the independent variables. Second, several factors also predict the outcomes of treatment outcome (cure and death) include socio-economic nutritional status and/or baseline of weight smoking and alcohol consumption, side effects during treatment, diabetic status, and additional micronutrient consumption during treatment.[9,10,12-14,16,20,25,31-41] Third, this study only involved pulmonary tuberculosis, while extra pulmonary tuberculosis may also be a significant predictor of treatment outcome.[15,20,29,42] However, we believe that potential selection bias was low because of the small drop out percentage (7%) and high rate of participation (88%), so that the study results have generalizability for others population.

CONFLICT OF INTEREST

No conflicts of interest declared.

ACKNOWLEDGMENTS

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Tocilizumab as a Treatment for 'Cytokine Storm Syndrome' in COVID-19: A Case Report

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ABSTRAK

Coronavirus disease 19 (COVID-19) yang disebabkan oleh Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), saat ini tengah menjadi permasalahan di dunia, terutama karena tingginya kecepatan transmisi dan manifestasi klinis yang beragam. Acute respiratory distress syndrome (ARDS) dan kegagalan multiorgan merupakan kejadian tersering yang ditemukan pada kasus berat COVID-19. Laporan kasus ini mendeskripsikan seorang pasien berusia 53 tahun yang didiagnosis dengan COVID-19. Evaluasi lebih lanjut dari pasien ini menunjukkan adanya peningkatan bermakna kadar IL-6 dalam darah disertai dengan hiperferitinemia, yang sesuai dengan karakteristik sindrom badai sitokin. Pasien diterapi dengan tocilizumah, sebuah antibodi monoklonal dan antagonis reseptor IL-6. Ikatan antara tocilizumab dan IL-6 secara efektif menghambat dan menangani sindrom badai sitokin. Meskipun laporan kasus ini melaporkan efektivitas tocilizumab dalam tata laksana sindrom badai sitokin, tocilizumab juga diketahui memiliki berbagai efek samping yang perlu dipantau secara ketat selama

pengobatan. Diperlukan uji klinis terkendali untuk mengevaluasi efektivitas dan keamanan pemberian tocilizumab pada subjek dengan karakteristik klinis yang bervariasi dan dengan jumlah subjek yang lebih banyak.

Kata kunci: *COVID-19, SARS-CoV-2, acute respiratory distress syndrome (ARDS), Tocilizumab.*

ABSTRACT

Coronavirus disease 19 (COVID-19) which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been a problem worldwide, particularly due to the high rate of transmission and wide range of clinical manifestations. Acute respiratory distress syndrome (ARDS) and multiorgan failure are the most common events observed in severe cases and can be fatal. Cytokine storm syndrome emerges as one of the possibilities for the development of ARDS and multiorgan failure in severe cases of COVID-19. This case report describes a case of a 53-year-old male patient who has been diagnosed with COVID-19. Further evaluation in this patient showed that there was a marked increase in IL-6 level in blood accompanied with hyperferritinemia, which was in accordance with the characteristic of cytokine storm syndrome. Patient was treated with tocilizumab, a monoclonal antibody and is an antagonist to IL-6 receptor. The binding between tocilizumab and IL-6 receptors effectively inhibit and manage cytokine storm syndrome. Although this case report reported the efficacy of tocilizumab in managing cytokine storm syndrome, tocilizumab has several adverse effects requiring close monitoring. Further clinical randomized control trial is required to evaluate the efficacy and safety of tocilizumab administration in participants with various clinical characteristics and greater number of subjects.

Keywords: *COVID-19, SARS-CoV-2, acute respiratory distress syndrome (ARDS), Tocilizumab.*

INTRODUCTION

Coronavirus disease 19 (COVID-19) which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), until now has been a problem worldwide. The high rate of transmission in COVID-19 causes the disease difficult to control. COVID-19 was first found in December 2019 and by 15th December 2020 this disease has caused 1,618,374 mortality worldwide.[1] Although most cases cause mild clinical manifestation, some cases may cause severe clinical manifestation and death. Acute respiratory distress syndrome (ARDS) and multiorgan failure are the most common events found in severe cases and become the cause of death in most cases.

Until recently, cytokine storm syndrome emerges as one of the possibilities for the development of ARDS and multiorgan failure in patients with COVID-19.[2] Cytokine storm syndrome is a systemic inflammatory response that can be instigated by many factors, including infection and medications. Cytokine storm syndrome can be found in disease with disruption of immune system or immune related therapy, such as chimeric antigen receptor (CAR) T cell therapy, and viral infection.[3] A study which was performed by Huang et al found that in critically ill COVID-19 patients, there was an increase in proinflammatory cytokine concentration, such as IL-6, IL-10, IL-7, IL-2 and IFN-γ.[4] IL-6 itself has an important role in inflammatory reaction and immune response. Based on the previous study, it is known that IL-6 is the most important cytokine in the occurrence of cytokine storm syndrome in COVID-19. Therefore, tocilizumab (TCZ) which is a humanize antibody to IL-6 receptor was considered as a treatment in severe cases of COVID-19 to decrease mortality rate.[5] In this article, we reported a COVID-19 case who experienced cytokine storm syndrome, prompting tocilizumab as a therapeutic option.

CASE ILLUSTRATION

A male patient, 53-year-old, was admitted with the chief complaint of fever in the past 1 week prior to hospital admission. Fever was felt intermittently. The patient also complained of muscle and joint pain. He also complained of pain in the lower right and left abdomen, accompanied with diarrhea 1 time/day. There was sore throat and mild dry cough which occurred

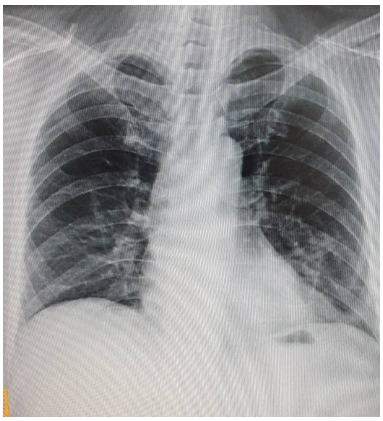

Figure 1. Chest X-ray, one day before admission. Result showing signs of pneumonia.

after 3 days. Complain of breathing difficulty was denied. On the third day of fever, patient underwent blood examination in the laboratory for dengue serology examination and obtained a negative result. Due to the persistent fever although without diarrhea, the patient underwent another blood test and chest x-ray. The results of chest x-ray examination showed signs of pneumonia (**Figure 1**). Chest CT revealed ground glass appearance (GGO), multifocal subpleural and fibro-parenchymal opacity in both lungs. He was further hospitalized.

Upon admission to the hospital, the patient was diagnosed as patient under surveillance of COVID-19. History of hypertension, diabetes, or cardiac disease was denied. History of allergy and other chronic disease was also denied. There was no other family member complaining similar symptoms. Physical and vital signs examination revealed that the patient was stable and there was no abnormality in general examination. Patient

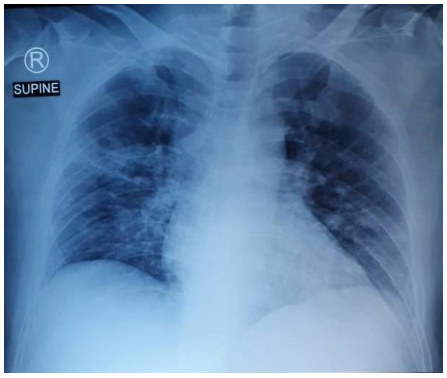

Figure 2. Chest X-ray, Day 4 admission. Result showing worsening signs of pneumonia.

was then hospitalized in isolation room.

During hospitalization, patient complained of intermittent fever. In the first three days of hospitalization, patient was afebrile. On day 4 of hospitalization, he felt intermittent fever for 4 days, with the highest recorded temperature was 38.9 ^{0}C. The patient also started to suffer from dry cough and occasional breathing difficulty particularly after physical activity, supported by the worsening of patient chest x-ray (**Figure 2**). Cough was usually felt after position changes, sometimes cough was accompanied with or without sputum. On hospitalization day-8, week-3 after the onset of fever, patient continuously had fever, body ache, and sleeping difficulty. During hospitalization, the patient did not have any gastrointestinal symptoms. Until hospitalization day-12, the fever condition was still intermittent, accompanied by cough and shortness of breath, but oxygen saturation was adequate with oxygen supplementation through nasal cannula 4-5 liter. Without oxygen supplementation, his oxygen saturation was 90-91%. However, based on observation every 6 hours, overall patient's hemodynamic condition is quite stable.

Several laboratory tests were performed to the patient. Complete blood count and differential count were still within normal range, although there was an increase in hematocrit to 38.8%, relative neutrophilia, and relative monocytosis. The relative increase in neutrophil and monocyte were in accordance with the increase of procalcitonin, quantitative CRP, and ferritin in infection or inflammation condition. Neutrophil-lymphocyte ratio (NLR) was initially increased from 6.35 and then it dropped to 4.94, before becoming back to normal normal 2.47. Ferritin serum examination revealed an increase in ferritin concentration 2277.08 ng/mL. The results of troponin and kidney function test were within normal limits. Liver function test showed an increase in AST to 41 U/L. CRP examination revealed a concentration of 7.1 mg/L in day 1 and continue to increase with highest CRP level was 95.5 mg/L. Additionally, patient also underwent plasma IL-6 level test and an increase in IL-6 with a value of 84.0 pg/mL was found. Serum ferritin examination showed an increase in ferritin level 2277.08 ng/mL. Patient also

underwent RT-PCR examination for SARS-CoV-2 and SARS-CoV-2 antibody examination, which revealed positive SARS-CoV-2 results and non-reactive SARS-CoV-2 antibody. Based on these clinical condition and laboratory findings, the patient was diagnosed with COVID-19 with cytokine storm syndrome.

Upon admission, the patient received azithromycin 500 mg o.d, hydroxychloroquine 400 mg p.o. b.i.d. continued with 400 mg p.o. o.d. dose, and oseltamivir 75 mg p.o. o.d. Oseltamivir was given for 3 days, but further continued with favipiravir as per protocol dose 800 mg b.i.d., continued with 400 mg b.i.d. dose for 2 weeks. Intravenous paracetamol drip was administered if his temperature was above 38.5 degree Celsius. Patient was also given Vitamin C 1000mg i.v. b.i.d., other multivitamin tablet p.o. o.d., vitamin D 1000 IU o.d, and Zinc 30 mg o.d. Before being hospitalized, patient experienced electrolyte disturbance, decreased potassium and sodium and received KCl drip. Patient also experienced hypocalcemia and was given calcium gluconate injection. During administration of hydroxychloroquine therapy, patient underwent EKG examination to monitor cardiac abnormalities, and during cardiology evaluation, no cardiac abnormality was found.

On hospitalization day-8, patient underwent blood coagulation system test. The patient had increased D-dimer and fibrinogen level with the result of 1080 mcg/mL and 700 mg/dL, respectively. (**Figure 3**). Based on these results, the patient was given enoxaparin as anticoagulant.

On day 10 of hospitalization, chest CT-scan without contrast was performed and showed worsening condition with further consolidation. This was in accordance with the typical appearance of pneumonia with fibrotic appearance in lower lobe and thickening of the right pleura.

On hospitalization day-10, patient was given anti-IL6, Tocilizumab or Actemra, and after administration of the 600 mg single dose tocilizumab, patient's condition ameliorated, fever subsides, cough and breathing difficulty gradually improves, until finally on day-18 the patient did not require supplemental oxygen. The patient was discharged on day-22 with good condition and normal laboratory parameters. Although RT-PCR from nasopharynx and oropharynx still showed positive results, the Ct (cycle threshold) value continue to increase, showing that the number of virus continue to decrease. Until week-6 after first complaint, RT-PCR from nasopharyngeal swab was still positive, but patient's clinical condition was good and improved, and the patient continued to do self-isolation. The chest x-ray taken before the patient was discharged also shown improvement (**Figure 4**). The patient's condition continued to

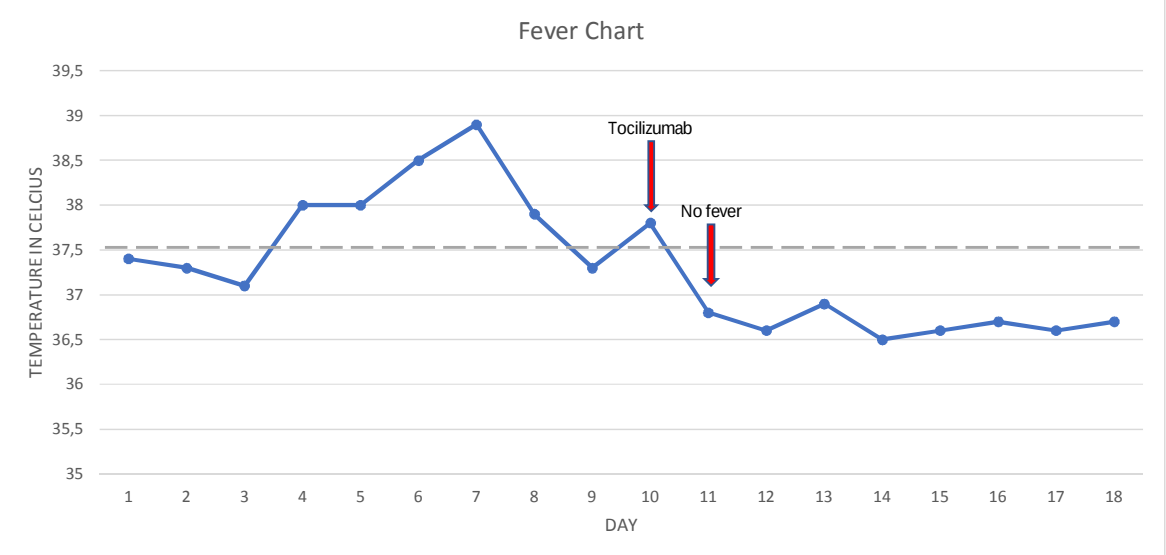

Figure 3. Fever patterns before and after treatment with Tocilizumab.

Table 1. Results of oxygen saturation and laboratory series

Tocilizumab ↓

Days of admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18
T(^{0}C)	37.4	37.3	37.1	38	38	38.5	38.9	37.9	37.3	37.8	36.8	36.6	36.9	36.5	36.6	36.7	36.6	36.7
RR (times/ min)	17	17	16	24	17	28	30	18	24	40	30	24	28	21	24	22	20	20
Peripheral oxygen saturation (%)	99	98	98	97	97	94	95	95	93	93	90	93	94	95	94	95	96	96
Neutrophil (x10^9/L)						80.8				74.3					65.7			
Lymphocyte (x10^9/L)						12.7				15					26.5			
ALT (U/L)	41									69					54			
AST (U/L)	28									93					94			
LDH (U/L)											319							
Natrium (meq/L)				133	128	134	133	130	132		**136**	136			135			
Total Calcium (mg/dL)				7.7			7.7		7.5		7.9				7.8			
Procalcitonin (nG/mL)	0.06						0.12				0.12							
CRP (mg/L)	7.1			10.3			75.4		95.5						4.3			
NLR							6.35			4.94					2.47			
PT (s)									13.4									
INR									1.02									
Fibrinogen									700									371
d-Dimer (ug/mL)									1080			1137			680			264
Ferritin (ng/ mL)			688.2						2277.08						865			
IL-6										84.0								
SARS-CoV-2 RT-PCR		Positive						Positive				Positive						
Antibody SARS-CoV-2		Non-reactive													Reactive IgM IgG			

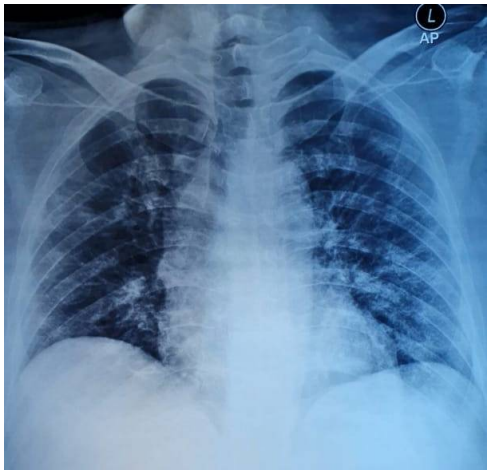

Figure 4. Chest X-Ray, Day 22. Result Showing Improving Signs of Pneumonia

improve and was able to carry on with normal activity 1 month after hospitalization with negative swab result.

DISCUSSION

COVID-19 is a highly transmitted infectious disease with various clinical manifestations, ranging from asymptomatic, mild pneumonia, severe pneumonia until critical clinical manifestation which causes death. Several studies reported that COVID-19 with severe manifestation showed an increase in proinflammatory cytokines causing cytokine storm syndrome.[2] Cytokine storm syndrome itself is marked by an increase in IL-6 level accompanied with hyperferritinemia[5].

In this case report, we presented a moderate COVID-19 case with cytokine storm syndrome which was marked by the increase in IL-6 level in the blood, hyperferritinemia with coagulation disorder, hypocalcemia and electrolyte disturbance. The patient was treated with tocilizumab. In this case, the patient showed clinical and laboratory parameters improvement after administration of tocilizumab. The most relieving lessons of this experience was that not only the fever subsided, but also the saturation improvement prevented this patient from being intubated and the need of mechanical ventilation. This finding was in accordance with previous study involving 21 severe and critically ill COVID-19 patients in China. In this retrospective study, it was found that administration of tocilizumab may improve clinical condition, which was supported with improvement of laboratory parameter such as decreased CRP and IL-6 level. Additionally, chest CT-scan also showed significant improvement after tocilizumab administration in almost all patients.[6] In this case, NLR may increase in early infection suggestive of systemic inflammatory response[7]. NLR examination has a sensitivity of 88% and specificity of 63.6% in determining the severity of COVID-19 [8]. Ferritin and CRP are acute phase proteins, which levels increase in infection or inflammatory condition.

Other study in China involving COVID-19 patients with more various clinical appearance, which were COVID-19 with moderate pneumonia, severe pneumonia, and critically ill patients. This study was performed in 15 patients and showed that after administration of tocilizumab, 80% of patients showed clinical improvement, decreased CRP and IL-6 levels. Administration of tocilizumab was considered to decrease or manage COVID-19 with cytokine storm syndrome.[9] In addition, another study was conducted in Italy involving 85 COVID-19 patients comparing 62 COVID-19 patients who were given tocilizumab and 23 patients receiving standard therapy of hydroxychloroquine, lopinavir, and ritonavir. Based on this study, it was found that the low dose tocilizumab administration might result in clinical improvement and decreased mortality in COVID-19 patients compared to patient who did not receive tocilizumab.[10]

Until now, the mechanism of cytokine storm syndrome in SARS-CoV-2 infection remains unknown. However, the incidence of cytokine storm syndrome is frequently associated with the increase in IL-6 level. IL-6 itself can be produced by almost all stromal and immune cells, such as B lymphocyte, T lymphocyte, macrophage, monocyte, dendritic cell, mast cell, and other non-lymphocyte cells, including fibroblast, endothelial cell, keratinocyte, glomerular mesangial cell, and tumor cell.[11-12] In SARS-CoV-2 infection, after the virus binds to the ACE-2 receptor in type II pneumocyte in the lungs, it will invade the cell and replicate resulting

in cellular apoptosis and necrosis. It will also trigger the inflammatory response, including the production of inflammatory response in the form of proinflammatory cytokine, macrophage and Th1 cell activation, followed by the production of IFN-γ, IL-17A, IL21, and IL-22 by neutrophil, Th17 cell, and $CD8^+$ cell. In normal condition, the production of proinflammatory cytokine is followed by the production of anti-inflammatory cytokine, so cytokine storm did not occur. Based on the study, the increase in IL-6 level in COVID-19 occurs because SARS-CoV-2 infects macrophage and cause the upregulation of IL-6 production and the decrease of interferon expressions. The increase in IL-6 will cause the rise in monocyte differentiation, B cell antigen-dependent differentiation modulation, IgG production by B cell, and Th2 response promotion by inhibiting Th1 polarization. Due to the SARS-CoV-2 invasion on pneumocytes and lung macrophages, local cytokine storm in COVID-19 patients is potentially higher than the systemic storm. Other studies reported that there was a strong correlation between IL-6 serum and the incidence of respiratory failure. This correlation is potentially stronger than the correlation of plasma IL-6 with the incidence of respiratory failure in ARDS (acute respiratory distress syndrome) due to other systemic sepsis, where plasma IL-6 is much higher than plasma IL-6 in COVID-19, but the lung lesion appearance and the respiratory failure can be less severe.[12] This explains that the respiratory failure in COVID-19 is more prominent than the fever, and this also explain the reason COVID-19 is more deadly. In this patient, the plasma IL-6 was 84 pg/ml, which was highly significant because the normal plasma IL-6 was 0 – 5 pg/ml or not more than 15 pg/ml. It can be imagined that the lung tissue IL-6 level was potentially much higher than 84 pg/mL in the plasma, and the lung damage is potentially severe. Based on a study, it was known that the increase of IL-6 level more than 80 pg/mL was correlated with higher risk to develop respiratory failure. The administration of anti-IL-6 may manage the cytokine storm syndrome which happen in COVID-19, either systemic or in the lungs.[13]

Tocilizumab is a monoclonal antibody and is an antagonist to IL-6 receptor. IL-6 will bind to the IL-6R receptor and form a complex, which will further bind to glycoprotein 130 (gp-130) signal transducer and stimulate the gene expression. IL-6R itself can be found not only in the transmembrane (mIL-6R) form, but also in the soluble (sIL-6R) form. These two forms of IL-6R will cause the signal transduction through different pathways, which are classic transduction and trans transduction pathway. In the classic transduction pathway, many cells did not respond to IL-6 signal due to the low expression of mIL-6R. Classic signal transduction is only limited to several cells, including macrophage, neutrophil, T lymphocyte, and other cells which express mIL-6R. In the cytokine storm syndrome due to COVID-19, there is an increase in IL-6 exceeding normal limits. This causes the high expression of mIL-6R and sIL-6R. In trans transduction pathway, sIL-6R itself can activate almost all cells in the body to regulate the pro-inflammatory reaction. Inhibition to trans transduction pathway has previously been known to be effective in managing several autoimmune diseases.[11,14-17] Tocilizumab itself is an anti-IL6 which can bind to both forms of IL-6R. The binding between tocilizumab and mIL-6R dan sIL-6R may inhibit the classic and trans transduction pathway, which effectively may inhibit and manage cytokine storm syndrome.[11,14,17]

Until now, tocilizumab has not received the approval to be used in the management of cytokine storm syndrome in COVID-19 in China. The recommendation of management of COVID-19 by WHO also stated that the use of tocilizumab in the management of COVID-19 is still limited to clinical trials. Nonetheless, "Diagnosis and treatment Plan of Novel Coronavirus Pneumonia (seventh trial edition)" in China recommends the use of tocilizumab in patient with wide lung lesion, in severe COVID-19 pneumonia, and in patients with high level of IL-6. Based on this recommendation, the recommended dose is 400 mg which is diluted in 100 mL NaCl 0.9% and given intravenously in 1 hour.[17]

Although the use of tocilizumab showed quite good efficacy in managing cytokine storm syndrome, there were several adverse effects which may happen due to the use of tocilizumab.

Based on United Stated FDA (Food and Drug Administration) there were several adverse effects which may appear: (1) serious infection: the most common infection is pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arteritis; (2) Gastrointestinal perforation which is reported as a complication of diverticulitis. Most patients who experienced gastrointestinal perforation use tocilizumab in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid, or methotrexate in the same time; (3) Infusion reaction: the most common reported adverse effects during administration are hypertension, headache, and skin reaction; (4) Anaphylaxis; this reaction is usually reported in the second to fourth administration of tocilizumab; and (5) laboratory parameter abnormality: such as thrombocytopenia, increased liver enzyme, and increased lipid profiles.[17,18]

CONCLUSION

Tocilizumab could be used as a therapy for cytokine storm syndrome in COVID-19 patients. However, the success of the treatment may be depending on the degree of COVID-19 severity. Further clinical randomized control trial is required to evaluate the efficacy and safety of tocilizumab administration in participants with various clinical characteristics and a greater number of subjects.

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A Beneficial Bipolar Hemiarthroplasty on a Centenarian in One Developing Country

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ABSTRAK

Fraktur pinggul geriatri sering terjadi, namun operasi pada pasien berusia 100 tahun jarang terjadi di Indonesia. Kami melaporkan artroplasti pada wanita 100 tahun dengan fraktur panggul kanan dan fraktur Colles kanan yang menguntungkannya tiga tahun hidup aktif dan berkualitas. Meskipun usianya sangat lanjut, pasien cukup mandiri, aktif, dan mobilitasnya baik. Oleh karena itu perencanaan pra-operasi dan rehabilitasi paska-operasi yang cermat disusun oleh tim geriatri medis dan non-medis yang komprehensif. Hemiarthroplasty bipolar tanpa semen cukup sempurna untuk patah tulang pinggul di bawah anestesi regional sementara patah tulang Colles dikelola dengan reduksi tertutup dan plesteran. Rehabilitasi dimulai pada Hari ke-2 dan dilanjutkan beberapa minggu setelah pulang. Pasien dapat bertahan hidup dan sehat sampai setelah 3 tahun operasi. Pembedahan bermanfaat bagi pasien berusia 100 tahun; demi kepentingan terbaik mobilitas dan kualitas hidup pasien. Usia saja tidak boleh membatasi keputusan pembedahan selama semua komorbiditas dikendalikan oleh tim geriatri medis dan non-medis yang komprehensif.

***Kata kunci**: cementless bipolar hemiarthroplasty, fraktur pinggul, usia lanjut, pembedahan.*

ABSTRACT

Geriatric hip fractures are common; however, surgery on a 100-year-old patient is rare in Indonesia. We report arthroplasty in 100-year-old woman with right hip fracture and right Colles fracture; which benefits her a three year of active and qualified life. Despite her age, the patient was quite independent, active, and mobile beforehand. Hence a meticulous preoperative planning and post-operative rehabilitation were structured by a comprehensive medic and non-medic geriatric team. Cementless bipolar hemiarthroplasty was perfectly sufficient for the hip fracture under regional anesthesia while the Colles fracture was managed with a close reduction and plastering. Rehabilitation was started on Day-2 and continued weeks after discharge. The patient is still alive and well 3 years after the surgery. Surgery is beneficial for the 100-year-old patient; it is in the best interests of the patient's mobility and quality of life. Age alone should not limit a surgical decision as long as all comorbidities are controlled by a comprehensive medic and non-medic geriatric team.

***Keywords**: cementless bipolar hemiarthroplasty, hip fracture, elderly, surgery.*

INTRODUCTION

Indonesia is a developing Asian country where there are only few 100 years old patients with hip fracture undergoing a surgery. The uncommonness of the cases was shown by the lack of reported data. From the socio-cultural point of view, there's little to no reasons that medical decisions such as surgery should be performed on a very old patient. The number of hip fractures among the elderly is expected to surpass 6 million by the year 2050 worldwide.[1,2] Geriatric hip fracture is highly burdening; not only is it a major morbidity, many of them never fully recover.[3-5] Instead, hip fracture is one of the major problems in the very old patient due to bedridden worsening factors.[4,5] By immaculate planning management, the sooner the surgery performed, the sooner patient back to usual active life, and skip the morbidity.[5,6]

When a 100-year old woman, who was still healthy and active, tripped and needed a major surgery, several medical and non-medical preparations should be convened. Quality of life of the patient is one of the most important things to consider in planning a treatment management.[5,6]

Our report discusses the benefit of surgery on a geriatric patient with a hip fracture contrary to the local socio-cultural beliefs that may prevent this medical procedure from being performed. This case report has been reported in line with the SCARE criteria.[7]

CASE ILLUSTRATION

A 100-year-old woman (Indonesian woman of Chinese descent), height 1.42 m, weight 39 kg, ASA II, and body mass index of 19.3 kg/m^2) was admitted in ER after a domestic fall on September 2013. Patient was compos mentis; her heart rate was 80 bpm and blood pressure were 150/80 mmHg. Patient had a history of mild hypertension and was on medication without hyperlipidemia, diabetes, nor cardiac arrhythmia. She was able to do daily activities independently before admission.

Patient felt pain on the right hip and wrist, both regions were swollen, deformed and had limitation of motion. The neurovascular and mental status were good. There were no other complaints associated with this injury.

X-ray of the hip lesion showed fracture of the trochanter of the right femur (AO classification 31-A1) and Colles fracture of the right wrist. Chest X-ray was normal, but ECG revealed minor mitral regurgitation.

Laboratory tests displayed within normal hematology value, insignificant liver and renal function, and all electrolytes were within normal value.

The thorough preparation involved a medic and paramedic incorporating team to convince the patient and the family about the benefits and the risks of the surgery and the necessary lengthy rehabilitation. Despite the commonly-perceived notoriety and the notion that doing surgery on a very old patient may potentially be useless and dangerous, the patient herself was willing to be mobile and able to enjoy her life again. The geriatric team prepared the informed consent form, explained and discussed the necessities and all possible risk factors of the treatment planning, the surgical procedure and anesthetic technique with the patient and the family.

Treatment planning, bipolar arthroplasty for right hip fracture, closed reduction and plastering for the right Colles fracture. Skin traction for the hip was applied one day before the surgery. The preoperative and postoperative X-ray(s) of the right wrist and hip are depicted in **Figure 1** and **2,** respectively.

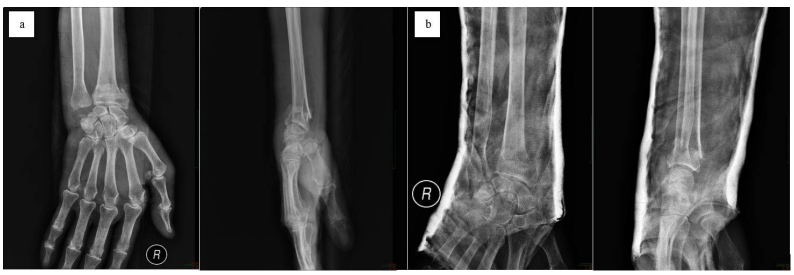

Figure 1. Colles fracture. (a) Right colles fracture before reduction (b) After reduction in circulair cast.

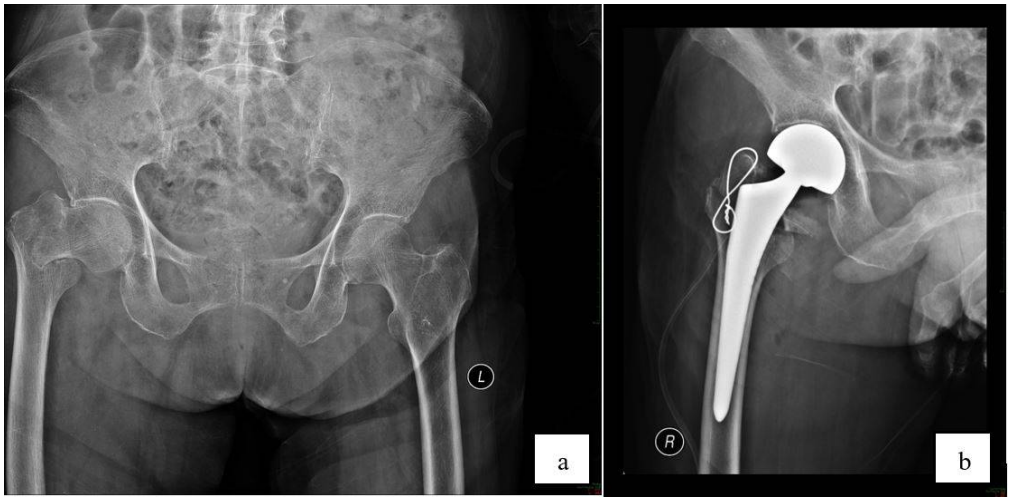

Figure 2. Hip Fracture. (a) X-ray of right fracture pertrochanter hip. (b) X-ray after bipolar arthroplasty and sanar wire augmentation.

Preoperative medication, the existent antihypertensive medication (amlodipine 5 mg p.o. o.d), celecoxib 40 mg i.v. o.d for analgesic and ceftriaxone 2 mg i.v. o.d. as prophylactic antibiotics.

Surgery was performed under regional anesthesia (epidural anesthesia) using Marcaine 0.5%. Cementless bipolar hemiarthroplasty was inserted by the Moore's posterior approach in lateral decubitus position. The trochanter mayor was fixated using wire.

There was no prosthesis instability nor leg length discrepancy, which were checked while in the OR immediately after the surgery.

The surgery took 120 minutes with 400 ml blood loss and a drain was inserted for 2 days evaluation. Hemoglobin post-surgery was 9.5 gr%; transfusion was not needed. From the recovery room, patient was admitted in ICU for overnight observation.

Post-operative medication, the prophylactic antibiotic ceftriaxone 1 g i.v. t.i.d. for 2 days. Analgesic was changed to Tramadol 50 mg i.v. b.i.d. Other medications were amlodipine 5 mg p.o. o.d., citicoline 500 mg p.o. t.i.d., omeprazole 20 mg i.v. b.i.d. for two days, and alprazolam 1 mg p.o. o.d. prn.

On the second day (Day 1 post-surgery), patient was transferred to the ward. Some insignificant predictable complications occurred, such as constipation, sleeping difficulties, and delirium due to dementia drugs. Gradual mobilization was started by the physiotherapy team. Patient was put on half sitting position while leaning on the head of the bed with limited range of motion (ROM) of the hip joint. The rehabilitation program for active and passive movement was held twice a day. Post-operative blood from drain was 180 ml, became minimal to less than 30 ml, and the drain was off by 2x24 hours post-surgery. Hemoglobin on Day 2 post-surgery was 10.5 gr%.

On the fourth day of post-surgery, the patient was encouraged to sit and increase her hip joint ROM. On the fifth day, the patient was trained to sit on the bedside and transferred to a chair or wheelchair. The rehabilitation process was done gradually by Log-rolling, sitting-standing, and partial weight bearing walking using U walker. The clinical photo of patient's rehabilitation process is depicted in **Figure 3**.

On the sixth day, the patient was discharged as scheduled owing to the good and significant recovery as well as the mobility progression. The distal perfusion and ROM evaluation of the Colles fracture were good with minimal VAS score (1-2). The plastering of the Colles fracture was kept for 5 days and then was changed into skin tight before discharge. All surgical-related medications were discontinued upon discharge. The patient's care-giver was her youngest daughter who stayed with her. The care-giver was taught to clean the wound areas and keep the rehabilitation program twice a day.

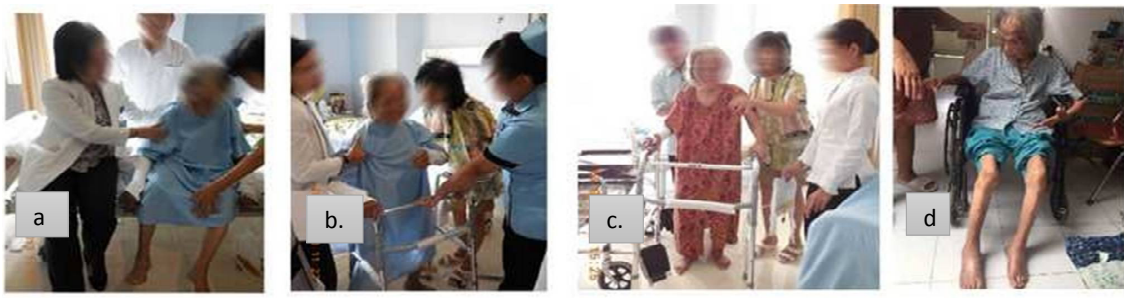

Figure 3. (a) (b) Sequences of rehabilitation 2nd after surgery, (c) 3rd day after operation, (d) 4 years after surgery.

Follow-ups were scheduled on the 2nd week for wound care and physiotherapy evaluation. Surgical wound was healed without any sign of skin inflammation. The VAS for hip and wrist was minimal (1-2). Physiotherapy was continued as scheduled.

Four weeks post-surgery, the hip joint was functioning well; good ROM without pain. The wrist was clinically union, well-functioning and the patient could hold the walker without pain; but the wrist x-ray showed minimal calluses and revealed shortening of the radial bone. The wrist cast was removed, and the patient felt fine. A rehabilitation physiotherapy program was continued to improve the range of motion of the wrist and the patient was also asked to continue mobilization with walker at home until 6-8 weeks.

A recent interview (2nd March 2017) with the patients' family revealed that the patient was still mobile and active until two years post-surgery (2015) without any complications. However, in the last years (2016-2017), her dementia and cataract worsened, which affected her activity; yet, she was otherwise in good health regarding her hip-related condition.

DISCUSSION

Hip fractures are very common among elderly patients due to osteoporosis and multiple associated diseases.[6] This type of fracture increases the risk of morbidity and mortality among the elderly.[2,3] Elderly people are frail, disabled and dependent.[8-10] Among the elderly, severe disability after acute hospitalization is most commonly caused by falls and hip fracture.[10,11]

In this case there are some comorbidities that were managed by the geriatric medical team. The meticulous pre-operative planning and post-operative rehabilitation as one medical decision were structured to minimize post-operative complications.[5,6,8] Regardless of the age, the patient was quite independent, active and mobile before the fracture; hence a comprehensive management incorporating the veracious surgical and anesthesia technique, the exact implant selecting, and immediate post-operative rehabilitation was taken into consideration.

People aged 90 years old or older are prone to suffer traumatic injuries that would cause hip fractures requiring care and rehabilitation. Furthermore, this age is associated with increased mortality and worse chance of functional recovery.[12] Even though the risks of complication are high, a study by Domenico et al. showed that patients 90 years of age or older with hip fracture achieved a surprisingly good post-operative outcome and returned home after rehabilitation.[13] In this case, the patient had a positive outcome due to a multidisciplinary approach and comprehensive care of the patient before, during, and after the surgery. In the absence of routine follow-up, complications after a hip hemiarthroplasty are frequently present; most of them require surgical reintervention.[14]

Cementless bipolar hemiarthroplasty was performed through Moore's posterior approach. Cementless type of prosthesis was chosen to decrease blood loss during operation. It also has a lower dislocation rate; therefore, the rehabilitation process could be done swiftly without limitations and with a lower risk of pulmonary embolism due to prosthetics.[8] The Austin-Moore Hemiarthroplasty has been used for more than 60 years and is frequently performed for dependent elderly patients.[15]

The result of the study conducted by Lin et al.[14] suggested that elderly patients who receive bipolar hemiarthroplasty may have a better rate of survival compared to those who receive unipolar hemiarthroplasty.[15] Some studies suggest that cemented prosthesis could reduce postoperative thigh pain, aseptic loosening, and the incidence of periprosthetic fracture.[16,17] However, uncemented prostheses are believed by some surgeons to be able to eliminate cement-related complications and mortality and ; shorten surgery time, thus reducing complications that may arise after the surgery.[18,19] The Colles fracture was managed by a closed reduction and plastering to decrease the surgery time. Plastering would be changed into skin tight cast one week later, which then would be continued for four weeks, when there's a sign of clinical healing. Unstable distal radius fractures (Colles fracture) can be treated with closed reduction and cast application in low-demand elderly patients to avoid risks and complications of surgery.[20] Although there was malunion (4 weeks post-operative in X-ray perspective), but the wrist itself is in good function and painless when the patient held her walker.

The geriatric medic and non-medic team are very important; they are required to assess medical problems, to minimize risk of complications that may arise before, during, and after the surgery. The geriatric team was also involved since the first time in delivering informed consent and in discussing the non-medical issues as well. Based on the research results provided by Domenico et.al., a comprehensive geriatric assessment combined with a good multidisciplinary approach could provide a positive outcome for the elderly.[13] The short-term outcome of surgical management for Asian nonagenarian with hip fractures is favorable in selected patients.[21] The positive post-operative condition of the patient was also due to the comprehensive rehabilitation management during recovery, and the utmost supports from the family to keep the patient mobile and active, irrespective of her age.

This case is reported to inspire medical professionals in Asian developing countries that performing surgery on an elderly patient is possible, or even mandatory as long as the case is devoid of absolute contraindications. A good and comprehensive geriatric team is a must.

CONCLUSION

Performing a Bipolar Hemiarthroplasty in a previously healthy, active, and mobile 100year-old patient with hip fracture is a highly recommended medical decision. Age alone should not limit a surgical decision as long as all comorbidities are controlled, and complications are prevented by a comprehensive medic and non-medic geriatric team.

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Thrombotic Thrombocytopenic Purpura in Dengue Fever

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ABSTRAK

Purpura trombositopenik trombotik adalah kondisi medis yang jarang tetapi mengancam jiwa. Pengenalan dini dan pengobatan purpura trombositopenik trombotik penting terutama pada pasien yang tidak datang dengan pentad klasik untuk mengurangi angka kematian yang tinggi. Di sini, kami menggambarkan kasus pasien yang tidak memenuhi fitur pentad klasik purpura trombositopenik trombotik yang diinduksi oleh demam berdarah. Gambaran darah lengkap awal pasien tidak memiliki semua ciri khas anemia hemolitik mikroangiopati tetapi ada sel darah merah yang terfragmentasi. Namun, bahkan sejumlah kecil sel darah merah yang terfragmentasi dalam darah tepi harus mengingatkan dokter tentang kemungkinan diagnosis purpura trombositopenik trombotik bersama dengan gejala lainnya. Lebih lanjut, tanda dan gejala purpura trombositopenik trombotik dan demam berdarah dapat tumpang tindih seperti demam, trombositopenia, defisit neurologis yang menyerupai ensefalopati dengue, dan cedera ginjal akut yang diinduksi dengue.

Keywords: *acute kidney injury, ADAMTS13, dengue fever, plasma exchange, thrombotic thrombocytopenic purpura.*

ABSTRACT

Thrombotic thrombocytopenic purpura is a rare but life threatening medical condition. Early recognition and treatment of thrombotic thrombocytopenic purpura is important especially in patients who do not present with the classic pentad to reduce the high mortality. Herein, we describe a case of a patient who does not fulfil the classic pentad features thrombotic thrombocytopenic purpura that was induced by dengue fever. The patients' initial full blood picture did not have all the typical features of microangiopathic haemolytic anaemia but there were fragmented red blood cells. However, even a small number of fragmented red blood cells in the peripheral blood should alert physicians of the possible diagnosis of thrombotic thrombocytopenic purpura together with other symptoms. Furthermore, signs and symptoms of thrombotic thrombocytopenic purpura and dengue fever can overlap such as fever, thrombocytopenia, neurological deficit mimicking dengue encephalopathy and dengue induced acute kidney injury.

***Keywords*:** *acute kidney injury, ADAMTS13, dengue fever, plasma exchange, thrombotic thrombocytopenic purpura.*

INTRODUCTION

Thrombotic thrombocytopenic purpura is a rare condition caused by spontaneous platelet aggregation when ultra large multimers of von Willebrand factor are not cleaved appropriately in the absence of ADAMTS13.[1] The incidence of thrombotic thrombocytopenic purpura in the United States is 4 to 6 per million of the population per year whereas in the United Kingdom, it is 6 cases per million per year.[1] The classical pentad of thrombotic thrombocytopenic purpura are thrombocytopenia, fever, neurological symptoms, renal dysfunction and microangiopathic haemolysis. Thrombotic thrombocytopenic purpura can be idiopathic, autoimmune related or secondary. Secondary thrombotic thrombocytopenic purpura could be due infections, malignancy, drug induced or pregnancy associated. Infections associated with thrombotic thrombocytopenic purpura include human immunodeficiency virus, *Mycoplasma pneumoniae*, *Legionella pneumophila* and hepatitis C. There are a few published case reports of dengue fever with thrombotic thrombocytopenic purpura and is becoming an increasingly recognized phenomenon. Both these conditions can cause significant mortality and morbidity if there is a delay in initiation of treatment.

CASE ILLUSTRATION

A 29 year-old man with no past medical history was brought to the emergency department by family members with a one week history of altered behaviour and aggression on the day of admission. The family report he has been talking irrelevantly and having auditory hallucinations for one week. Furthermore, he had a five day history of fever associated with diarrhoea, loss of appetite, lethargy and one episode of haemoptysis. He did not have any vomiting or abdominal pain. Unfortunately, as patient was confused, we could not get much history from the patient and family members could only give a limited history. There was no history of foreign travel.

He is an active smoker of 13 pack years and consumed alcohol socially. He had history of cannabis use but last used nine years ago according to the family. He denied taking traditional medications. He was separated from his wife and worked as a computer analyst.

On admission, his Glasgow Coma Scale was 14/15 (E4, V4, M6). He was unkempt and confused. There was no jaundice and peripheries were warm with capillary refill time < 2 seconds with good pulse volume. His temperature was 37.6˚C, pulse rate 126 beats per minute, blood pressure was 157/106 mmHg, respiratory rate of 18 breaths per minute and oxygen saturation of 97% on room air. Blood glucometer was 6.1 mmol/l. Cardiovascular and respiratory system examinations were unremarkable. On abdominal examination there was splenomegaly of 2 finger breaths below the left costal margin. He had a petechial rash over bilateral lower limbs. Neurological examination revealed no neck stiffness and photophobia. He was confused but able to obey commands and power was 5/5 bilaterally with normal reflexes and down going plantar response.

A full blood count revealed:- haemoglobin was 12.5 g/dL (13.5-17.4), white cell count of 3.1 x 10^9/L (4.1-11.4), with neutrophils 0.8 x 10^9/L (3.9-7.1), lymphocytes 1.7 x 10^9/L (1.8-4.8) and platelet count was 20 x 10^9/L (142- 350). Renal function revealed sodium 125 mmol/L (136- 145), potassium 4.1 mmol/L (3.5-5.1), urea 23.3 mmol/L (3.2- 7.4) and, creatinine 740.8umol/L (63.6- 110.5). Liver function test revealed bilirubin level of 18.7 umol/l (3.4-20.5). His coagulation profile was within normal limits.

Dengue serology was performed as it is endemic in this part of the world and as patient had thrombocytopenia and leucopenia and dengue non structural protein 1 antigen test was positive. Dengue serology Ig G and Ig M were negative.

Arterial blood gas was done due to renal insufficiency and blood gas showed pH of 7.348 with serum bicarbonate level of 19.2 mmol/L (22- 28). Serum lactate level was 2.7 mmol/L (0.5- 1.6). Urine examination revealed proteinuria and microscopic haematuria.

Thrombotic thrombocytopenic purpura was entertained as a diagnosis and therefore secondary causes including infections and autoantibody diseases needed to be excluded.

Hepatitis B surface antigen, anti- hepatitis C antibody and human immunodeficiency virus (HIV) antigen and antibody were non reactive. C3 level was slightly low with level of 89.5 mg/ dL (90- 180) and C4 was normal at 26.4 mg/ dL (10- 40). Serum antinuclear antibody was negative.

In view of thrombocytopenia and confusion, an urgent Computed tomography scan of the brain was performed to exclude any intracerebral bleeding which was normal. Ultrasound of the hepatobiliary system and kidney was done in view of renal insufficiency and was normal except for splenomegaly at 13.5 cm.

Repeat full blood count 8 hours later demonstrated a drop in haemoglobin to 8.0 g/dL (13.5-17.4) and further drop in platelet count to 8 x 109/L (142- 350). In view of thrombocytopenia and diagnosis of thrombotic thrombocytopenic purpura was entertained, further investigations including coagulation and full blood picture was requested. The initial full blood picture showed hypochromic microcytic red blood cells with occasional fragmented red cells seen. Platelet count was markedly reduced (1-2/ hpf). Lactate dehydrogenase (LDH) level was 3036 U/L (125-220). Reticulocyte count was 0.3% (0.5- 2.5). Direct coombs test was negative. Diagnosis of thrombotic thrombocytopenic purpura secondary to severe dengue was made.

Patient was started on plasma exchange of approximately of 3L fresh frozen plasma daily. He was also transfused 2 pints of packed cells. He also underwent one session of haemodialysis on day 3 of admission as he was oliguric with worsening of his renal function. At the same time he received supportive treatment of blood transfusion with strict monitoring of input and output as part of fluid therapy in dengue management.

Follow up full blood picture on day 4 of admission showed there were spherocytes and microspherocytes seen with schistocytes, few target cells and blister cells seen. However, his clinical condition had improved by the second day and was fully alert, conscious and coherent. He was not confused at all. Infact the patient felt so well, that he wanted to be discharged even though his renal function had not normalized. After five plasma exchanges, his serum creatinine was 419.8umol/L (63.6- 110.5) and platelet count 123x 109/L (142- 350) with haemoglobin of 7.1 g/ dL (13.5-17.4) but stable.

He took discharge against medical advice after being counselled and assessed by a patient psychiatrist who deemed him competent. The patient subsequently did not turn up for follow up.

DISCUSSION

Thrombotic thrombocytopenic purpura is rare condition but has a high morbidity and mortality and therefore treatment has to be instituted early.[1] However, the first priority is to recognize and diagnose thrombotic thrombocytopenic purpura. Diagnosis of thrombotic thrombocytopenic purpura is made when at least 2 of the major criteria for diagnosis (microangiopathic haemolytic anaemia - MAHA, neurologic signs and thrombocytopenia) are associated with at least 2 minor criteria (fever, renal changes, and presence of thrombi in the circulation).[2] However, thrombotic thrombocytopenic purpura is still a diagnosis according to clinical history, physical examination and blood film. Thrombotic thrombocytopenic purpura can present without the full pentad with up to 35% of patients at presentation do not have renal impairment, neurological signs and fever.[1]

Diagnosis of thrombotic thrombocytopenic purpura can be very difficult, as there is clinical overlap with other thrombotic microangiopathy and autoimmune diseases and can sometimes be similar to haemolytic uraemic syndrome (HUS). Secondary thrombotic thrombocytopenic purpura can occur following infections, malignancy, drug induced and pregnancy associated.

Recently the criteria for thrombotic thrombocytopenic purpura has been revised in view of highly preventable early death in this clinical condition should treatment been given early. However, this may lead to increasing referral of other thrombotic microangiopathy. According to the revised diagnostic criteria, with the presence of thrombocytopenia and MAHA alone, thrombotic thrombocytopenic purpura must be considered and plasma exchange should be initiated as soon as possible, preferably within

4-8 hours in the absence of other identifiable cause.[3]

In our patient the diagnosis of thrombotic thrombocytopenic purpura was made based on clinical presentation, and laboratory investigations and he fulfilled 4 criteria, ie. thrombocytopenia, neurologic signs, fever and renal impairment. However, all these could be due to purely dengue with dengue encephalopathy and acute kidney injury due to dengue. Acute kidney injury in dengue fever can be due to acute tubular necrosis, glomerulopathy, nephrotic syndrome or even haemolytic uraemic syndrome.[4,5] Dengue was confirmed on the laboratory investigations. We treated the patients as thrombotic thrombocytopenic purpura secondary to dengue fever based on the presence of few fragmented red blood cells on the full blood film and the rapid drop in the haemoglobin and elevated lactate dehydrogenase.

The treatment of dengue fever is supportive whereas if thrombotic thrombocytopenic purpura is suspected then plasma exchange needs to be initiated early. We initiated plasma exchange and there was a rapid improvement in the patients' neurological condition.

Our patient had secondary thrombotic thrombocytopenic purpura whereas in the cases of acquired thrombotic thrombocytopenic purpura, treatment not only involves plasma exchange but also steroids and immunosuppressive therapy.[1] In thrombotic thrombocytopenic purpura, inhibition of ADAMTS13 activity is by autoantibodies that appear transiently as a result of disturbances between normal platelet-endothelium interaction. Therefore in thrombotic thrombocytopenic purpura, ADAMTS13 assays would help to confirm the diagnosis however it takes time for the results to be available.[1] We did not perform ADAMTS13 as it is not readily available at our institution and would take a few days for the results to be available. Duration of treatment was made on patient's clinical presentation.

There has been a few reported case of dengue with haemolytic uraemic syndrome. Wan et al[5] reported haemolytic uraemic syndrome with dengue viral infection and their patient was dialysis dependent after recovery from dengue fever. This was one of our differential diagnosis but we felt the patient erred towards thrombotic thrombocytopenic purpura in view of the predominant of neurologic involvement whereas haemolytic uraemic syndrome kidney involvement is dominant.[6] Thrombotic thrombocytopenic purpura is also reportedly to have more severe thrombocytopenia (<30x109/L) compared to haemolytic uraemic syndrome.[6]

Plasma exchange removes ADAMTS13 autoantibodies and replaces ADAMTS13 in thrombotic thrombocytopenic purpura.[7] The exact incidence of thrombotic thrombocytopenic purpura in dengue fever is not documented but there are a few case reports in countries where it is pandemic such as India.[7,8] In some of these reports they did measure ADAMTS13 and reported the mechanism of reduction in ADAMTS13 level was caused by the anti-ADAMTS13 IgG from dengue fever has been potentially similar to idiopathic thrombotic thrombocytopenic purpura TTP.[7] Gavali et al.[8] described a case of thrombotic thrombocytopenic purpura in dengue viral infection who was treated with plasma exchange and rituximab injection. The patient recovered completely and there was no recurrence after 6 months of follow up. There is another case of dengue fever- induced thrombotic microangiopathy reported by Bhargava et al, of which this patient has kidney biopsy proven features of thrombotic microangiopathy.[9] However, this patient was treated with haemodialysis without plasma exchange and the patient was followed up for 9 months post- discharge, she recovered well with normal renal function.

The possible causes of development of ADAMTS13 inhibitor include endothelial cell damage or stimulation by dengue fever which remains undetermined and needs further study.[7] This may explain why Bhargava et al.[9] did not do plasma exchange and their patient recovered spontaneously. In our patient, in view of the neurological involvement, we opted to treat with plasma exchange.

CONCLUSION

TTP in dengue is becoming increasing recognised and clinicians need to have a high

index of suspicion as the clinical features may overlap.

CONFLICT OF INTEREST

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Type 2 Diabetes Mellitus and Cognitive Impairment

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ABSTRAK

Diabetes melitus tipe 2 (DM T2) sangat terkait dengan kinerja yang lebih rendah pada beberapa domain fungsi kognitif dan dengan kelainan struktural otak. Dengan meningkatnya epidemi diabetes dan populasi yang menua, komplikasi saraf diabetes diperkirakan akan meningkat dan menjadi tantangan bagi implikasi kesehatan di masa depan. Memahami patofisiologi, faktor yang terkait dengan komplikasi ini, manifestasi gangguan kognitif dan berbagai penanda metabolik dan neuroradiologis yang mencerminkan kondisi patologis yang sangat penting dalam pengelolaan komplikasi DM T2. Ulasan ini akan membahas secara singkat aspek penting dari gangguan kognitif pada DMT2.

Kata kunci: *diabetes mellitus tipe 2, gangguan kognitif.*

ABSTRACT

Type 2 diabetes mellitus (T2DM) is strongly associated with lower performance on multiple domains of cognitive function and with structural abnormalities of the brain. With the growing epidemic of diabetes and aging population, neural complications of diabetes are expected to rise and becoming a challenge for future health implications. Understanding pathophysiology, factors associated with this complication, manifestation of cognitive impairment and various metabolic and neuroradiologic markers suggestive of this pathologic condition is crucial for proper management of this potentially debilitating complication of T2DM. This review will discuss briefly important aspects of cognitive impairment in T2DM.

Keywords: *type 2 diabetes mellitus, cognitive impairment.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycaemia, insulin resistance, and relative insulin deficiency. Currently there are 366 million people with diabetes mellitus world-wide, with more than 23 million people live in the United States. This number will reach the number 552 million by 2030. Type 2 DM is associated with many chronic complications, involving many organs including brain and nervous system.[1] Central nervous system-related complications of diabetes has been known for more than 100 years by researchers and clinicians as people with diabetes frequently complained of worsen memory and attention.[2]

Existing evidence suggested that T2DM was strongly associated with reduced performance on multiple domains of cognitive function and with structural abnormalities in the brain.[1,2] Cognitive decline in this case can manifest as mild cognitive impairment (MCI), Alzheimer's disease (AD), vascular dementia (VD) and many other form of dementias as measured by neuropsychological testing compared to non-diabetic controls. T2DM is associated with 50% increased risk of dementia.[2]

In a longitudinal studies, diabetes in midlife was associated with a 19% greater cognitive decline over 20 years compared with no diabetes in the ARIC study cohort. In a large prospective population-based cohort study of more than 6000 elderly subjects, T2DM almost doubled the risk of dementia.[2] Mayeda et al.[3] conducted a 10 year cohort study involving 1617 non-dementia older participants from Sacramento Area Latino Study on Aging. After adjusting for competing risk of death, either treated or untreated diabetes patients showed an increased risk of dementia/ mild cognitive impairment compared to healthy control group. Another meta-analysis estimated that T2DM people have a relative risk of vascular dementia of 2.5 (95% CI 2.1-3.0) and that of Alzheimer disease is 1.5 (95% CI 1.2-1.8) relative to individuals without diabetes.[4] Of the kinds of dementia, Alzheimer's disease (AD) is the most prevalent pathology. Clinically, AD is characterized by the loss of memory, change in personality and other cognitive functions necessary to perform complex daily activities. Alzheimer's disease (AD) is estimated to cost American society of 214 billion dollars in direct medical expenses, and is predicted to reach 1.2 trillion dollars by 2050.[5]

FACTORS ASSOCIATED WITH COGNITIVE IMPAIRMENT

Cognitive decline in T2DM has been associated with duration of diabetes, poor glycemic control, obesity, retinopathy and some other factors. These factors promote cognitive decline by some mecahnism: chronic hyperglycemia causing osmotic insults, oxidative stress, formation of advanced glycation end products (AGEs), activation of deleterious microglia and other mechanisms. All these factors load to direct toxicity on neurons.[6] Morris et al.[7] used data from Alzheimer's disease neuroimaging initiative (ADNI) to assess the impact of baseline glycemic status (fasting glucose) on cognitive performance and brain structure in MCI subjects. Changes in clinical dementia rating-sum of boxes, cognitive performance testing (global cognition), brain volume (whole brain and hippocampal volume), fluorodeoxyglucose-positron emission tomography and conversion to AD were assessed. Subjects with normoglycemia at baseline had less functional and global cognitive decline over 2 years; less whole brain volume loss and lower conversion from MCI to AD compared to subjects with impaired glycemia. This study suggested the role of glycemic control on cognitive decline in T2DM. A multivariate regression analysis found that HbA1C level was the only significant predictor of hippocampal atrophy in T2DM patients. However, in the ACCORD-MIND sub-study, there was no difference of cognitive performance or brain MRI outcomes between intensive glycemic control group compared with standard glycemic control group after 80 months of follow-up.[8] Another study linked obesity as a significant predictor of smaller hippocampal volume in T2DM.[9] In the ACCORD-Eye substudies of ACCORD-Mind, there was an association between baseline diabetic retinopathy and severity of retinopathy with decline in global cognitive function and processing speed over 40 months follow-up. This association was due to the similarity of embriology and anatomy between retinal and cerebral small blood vessels, causing vulnerability of both organs to the vascular factors such as T2DM.[2]

PATOPHYSIOLOGY

The pathophysiology of cognitive impairment in diabetes is still not fully understood. However, until now the most important mechanism underlying this condition is insulin signaling dysfunction leading to failure of glucose absorption in the neurons needed for energy production. Studies in AD revealed that this failure is associated with many mechanisms, such as insulin resistance, insulin growth

factor (IGF) signaling, inflammatory response, oxidative stress, glycogen synthase kinase 3β (GSK3β) signaling mechanism, amyloid beta (Aβ) formation from amyloid precursor protein (APP), neurofibrillary tangle formation, and acetylcholine esterase activity regulation.[1] Insulin resistance as a key link between type 2 DM and cognitive impairment refers to a condition where brain tissues do not respond sufficiently to physiological insulin concentration. Usually early type 2 DM patients have hyperinsulinemia but poor insulin sensitivity.[5] Long-term consequences of insulin resistance states include cellular energy failure, elevated plasma lipids, and hypertension.[10]

Secreted by pancreatic beta cells, insulin enters the central nervous system by crossing the blood-brain barrier.[5] Like in most organ systems, insulin and insulin-like growth factors (IGFs) play many important roles for optimal brain functions. They maintain homeostasis, energy metabolism and cell survival and support neuronal plasticity and cholinergic functions needed mostly for learning, memory and myelin maintenance.[10] In adipocytes and myocites, insulin regulates glucose transport by controlling translocation of the glucose transporter 4 ($Glut_4$).[5] In the brain, the virtually same mechanism of insulin and IGF signal transduction regulates metabolic activities. $Glut_4$ mediates glucose uptake in the brain tissue for energy production, which is abundantly expressed along with insulin receptors in the medial temporal lobe and other targets of AD. Both of this protein regulate glucose utilization and ATP production in the brain tissue. Impairment of these signaling, caused by receptor resistance or ligand deficiency will disrupt energy balance and disturb networks that support a broad range of brain functions.[10] Besides, this impairment makes neurons more vulnerable to metabolic stress, thus accelerating neuronal dysfunction.[5]

Both neurons and glia cells of the brain have insulin receptor (InsR) with more concentrated in neurons relative to glial cells and are especially high in post-synaptic densities. The areas with the highest density of insulin receptors are hippocampus, hypothalamus, cerebral cortex and olfactory bulb. Insulin binds to the extacellular α-subunit of InsR, resulting in autophosphorylation of the intracellular β-subunit. Activated InsR will activate and phosphorylates intracellular substrates especially several tyrosine residues on insulin receptor substrate (IRS) and Shc. These phospho-tyrosine residues are important for IRS 1 and 2 for initiating several signaling cascades such as phosphatidylinositol 3-kinase (PI3K), GSK3β signaling, mithochondrial regulation for energy production and etc. Phosphorylated tyrosine residues on IRS and Shc then recruit downstream signaling molecules containing Src homology 2 (SH2) domains, such as the p85 subunit of phosphatidylinositol 3 kinase (PI3K) which activates Akt-mediated signaling, and growth factor receptor-binding protein 2 (Grb2), which leads to the activation of mitogen-activated protein kinase (MAPK) signaling pathway. PI3K is associated with almost all of the metabolic actions of insulin.[1,5]

Akt molecules (Akt1, Akt2, and Akt3) is a serine/threonine kinase activated by PI3K downstream of growth factors and various cellular stimuli. Akt mediates the bulk of insulins action, including glycogen, lipid, and protein syhthesis, cell survival, and the anti-inflammatory response. The alteration or inactivation of Akt activity is one of the key characteristics of insulin resistance. Glut4 translocation is closely correlated with Akt2 activation through insulin-activated PI3K signals in adipocytes. Patients with type 2 DM have reduced Akt activation of adipocytes and skeletal muscle, leading to many damaging effects on neurons and glial cells. IRS proteins contain over 20 tyrosine residues and more than 50 potential serine/threonine phosphorylation sites. Activation of serine/threonine sites by phosphorylation will inhibit insulin signaling by antagonizing tyrosine phosphorylation. Multiple IRS serine kinases are activated in IR states, resulting in increased IRS serine phosphorylation and subsequently impaired insulin signaling. Decreased insulin signaling, including altered kinase activity and IRS expression, is getting worse with disease progression. In AD, interestingly the brain regions with the highest densities of InsR such as hippocampus and temporal lobe are also

the major targets of neurodegeneration in AD. Therefore insulin resistance in the brain can have profound effect on cognitive impairment and the development of AD. This condition exists not only in T2D, but also in the other insulin resistance states such as obesity, either in human or animal studies.[5]

MANIFESTATION OF COGNITIVE IMPAIRMENT IN T2DM PATIENTS

Data from prospective studies have shown that many people with T2DM perform less well than controls in the cognitive domains on information-processing speed, memory, attention and executive function. A longitudinal ARIC study showed cognitive decline in T2DM primarily in the domains of processing speed and executive function. Some studies have also shown change in mental flexibility and global cognitive function.[2] A case control study investigating drain volume abnormalities in older T2DM patients revealed a worse processing speed and memory performance in T2DM group compared with control subjects.[12] A 4 year cohort study conducted by Van den Berg *et al.* on non-demented T2DM patients found moderate decrements in information-processing speed and executive functions compared with controls at both of the baseline and the 4 year follow-up examination; however no evidence of accelerated cognitive decline over 3-6 years of follow up in T2DM groups.[13] On the contrary, other studies have showed accelerated decline in cognitive function over a follow up of 3-6 years in subjects with T2DM.[2]

In a large nationally representative cohort, The National Health and Aging Trends Study in US, 7605 elder participants were enrolled to complete immediate and delayed recall word list learning tests and Clock Drawing Test. In this study, analysis showed that baseline DM diagnosis was associated with decline on immediate and delayed word recall and the Clock Drawing Test. DM also predicted the incidence of dementia in older age groups at baseline.[14]

MARKERS OF COGNITIVE IMPAIRMENT IN T2DM

Metabolic Markers

The prominent hypothesis mediating T2DM with cognitive impairment is peripheral insulin resistance that promotes cognitive impairment by causing brain insulin resistance. Insulin resistance with dysregulated lipid metabolism leads to an increase in inflammation, cytotoxic lipid production, oxidative and endoplasmic reticulum stress, and worsening of insulin resistance. The role of cytotoxic ceramides that can promote inflammation, oxidative stress and insulin resistance are being investigated. Ceramides generated in liver or visceral fat can leak into peripheral blood because of local cellular injury or death, cross the blood-brain barrier, and initiate or propagate a cascade of neurodegeneration mediated by brain insulin resistance, inflammation, stress, and cell death.[10]

T2DM is associated with increased oxidative stress as a result of hyperglycemia and insulin resistance state. This systemic condition also involves the brain and cause pathological conditions affecting cognitive function such as proinflammatory networks causing organelle dysfunction, amyloid beta polypeptide precursor (AβPP) expression, neurotoxic fibrils production, activation of GSK-3β pathway which promotes tau phosphorylation leading to deposition of this pathologic substances.[10] There are many metabolic markers associated with oxidative stress, one of which is malondialdehyde.[15] Inflammation associated with obesity may contribute to hippocampal dysfunction and cognitive impairment. Besides, the hyperglycemia-associated production of reactive oxygen species and lipotoxicity leads to microvascular and macrovascular damage. In addition they may mediate T2DM and cognitive decline.[9]

Hyperglycemia can cause accumulation of advanced glycation endproducts (AGEs) leading to reactive oxygen species generation and cell damage. AGEs are peptide/protein molecules formed as a result of the Maillard reaction. These AGEs promote amyloid oligomer aggregation

and involve the formation AD neurotoxicity. AGE products produce superoxide and H_2O_2 resulting in lipid peroxidation and cell damage in the brain. The increase in free radicals in T2DM may be caused by varying levels of antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (PSH-Px), and catalase (CAT). This imbalance in prooxidants and antioxidants causes oxidative stress in T2DM and AD. Lipid peroxidation can occur in the brain tissue because of human brain gas with abundant peroxidizable polyunsaturated fatty acids and the relative paucity of antioxidants and enzymes. Mitochondrial dysfunction caused by insulin resistance triggers inflammation response. Insulin resistance increases the levels of cytokines such as IL-6, IL-1β and IL-18, TNF-α, α-1-antichymotrypsin and C-reactive protein.[1]

Plasma homocysteine has been associated with an increased risk for cardiovascular events in type 2 diabetic patients independent of conventional risk factors. In a cross sectional study conducted in Nigeria including 70 patients with T2DM and 30 healthy controls found a significant increased level of plasma homocysteine in patients with T2DM compared to healthy control subjects.[16] A cross-sectional study including 1276 Japanese showed that estimated glomerular filtration rate (eGFR) dan serum creatinin level were strongly associated with homocysteine.[17] A descriptive case series study conducted in Pakistan found that chronic poor metabolic control of diabetes mellitus is associated with elevation of plasma homocysteine concentration. This study included 70 T2DM patients with 48 of them showed hyperhomocysteinemia condition.[18] In addition in a meta-analysis conducted by Huang et al.[19] showed a strong evidence on the causal association of homocysteine level with the development of T2DM. Some studies have reported the association of homocysteine and T2DM-related cognitive impairment. Tian et al.[20] investigated this association and found that increased plasma homocysteine level was significantly related to T2DM-associated mild cognitive impairment (MCI), especially executive dysfunction. This study include 140 patients with mild cognitive impairment and 145 healthy cognition controls. The MCI group exhibited significantly higher plasma total homocystein levels than control group.

Neuroradiologic Markers

T2DM alters brain function and structures. Many studies have shown associations of diabetes mellitus with volume abnormalities of brain. Brain regional volume abnormalities have been studied intensively. T2DM is associated with global brain atrophy and increased burden of small-vessel disease. Results of studies identified consistent relationship between T2DM and cortical and subcortical atrophy, especially the temporal lobes. Hippocampus and amygdala atrophy was also consistently associated with T2DM. Zhang *et al* conducted a study to evaluate brain gray matter (GM) volume changes in T2DM patients and healthy control using voxel-based morphometry (VBM) based on MRI data. T2DM patients both with and without mild cognitive impairment showed significantly decreased total GM volume. Furthermore, compared with healthy controls, T2DM patients without MCI also exhibited extensively decreased GM volume, including the superior and middle temporal gyrus (MTG), the superior and medial frontal gyrus and the middle occipital gyrus. This study concluded the hypothesis that brain structural changes in several regions of the brain underlie transition from normal cognition to MCI in T2DM patients.[21]

A case-control study in older individuals by Reijmer et al.[12] was conducted to investigate the association of T2DM with microstructural abnormalties in specific white matter tracts and relation of this structural abnormalities with cognitive functioning. Using 3 Tesla diffusion-weighted MRI scan and detailed cognitive assessment, 35 non-demented T2DM patients and 35 matched control subjects showed microstructural abnormalities in various white matter pathways in T2DM patients. And these abnormalities were related to worse cognitive functioning, primarily slowing information-processing speed and memory performance. Besides volumetry and microstructural abnormalities, the other radiology markers

associated with cognitive decline in T2DM were cerebral infarcts and microbleeds composed a pathology entity, cerebral microvascular disease.[9] T2DM cause microvascular disease throughout the body, including the brain tissue. The finding of progressive atrophy of medial temporal lobe, which houses the hippocampus, support this pathologic condition. Chronic microvascular injury caused by hyperglycemia-hyperinsulinemia is characterized by reactive proliferation of endhotelial cells, thickening of the intima, fibrosis of the media and narrowing of the lumens. Damaged blood vessels are leaky and permeable to toxins and contribute to increased frequencies of microhemorrhage and perivascular white matter tissue loss in T2DM and AD.

Despite most studies investigating brain abnormalities in T2DM focused on structural changes, functional imaging studies in conjunction with T2DM have been increasing. Those functional studies include cerebral blood flow measurement (CBF), glucose metabolism using PET, and resting-state functional MRI (rs-*f*MRI). Studies attempting to link T2DM to alterations in CBF showed mixed results. Initial studies found a reduction in CBF in T2DM patients relative to controls, but later studies with larger sample sizes showed inconsistent patterns of CBF change in T2DM patients. Additionally, measurement of CBF provides only a gross measurement of total blood intake, without reference to regional differences that may increase or decrease with disease pathology.[22]

Another novel marker associated with cognitive impairment is sympathovagal imbalance (SVI). It has been reported to be associated with metabolic derangements in T2DM together with autonomic dysregulation and decreased heart rate variability (HRV). A

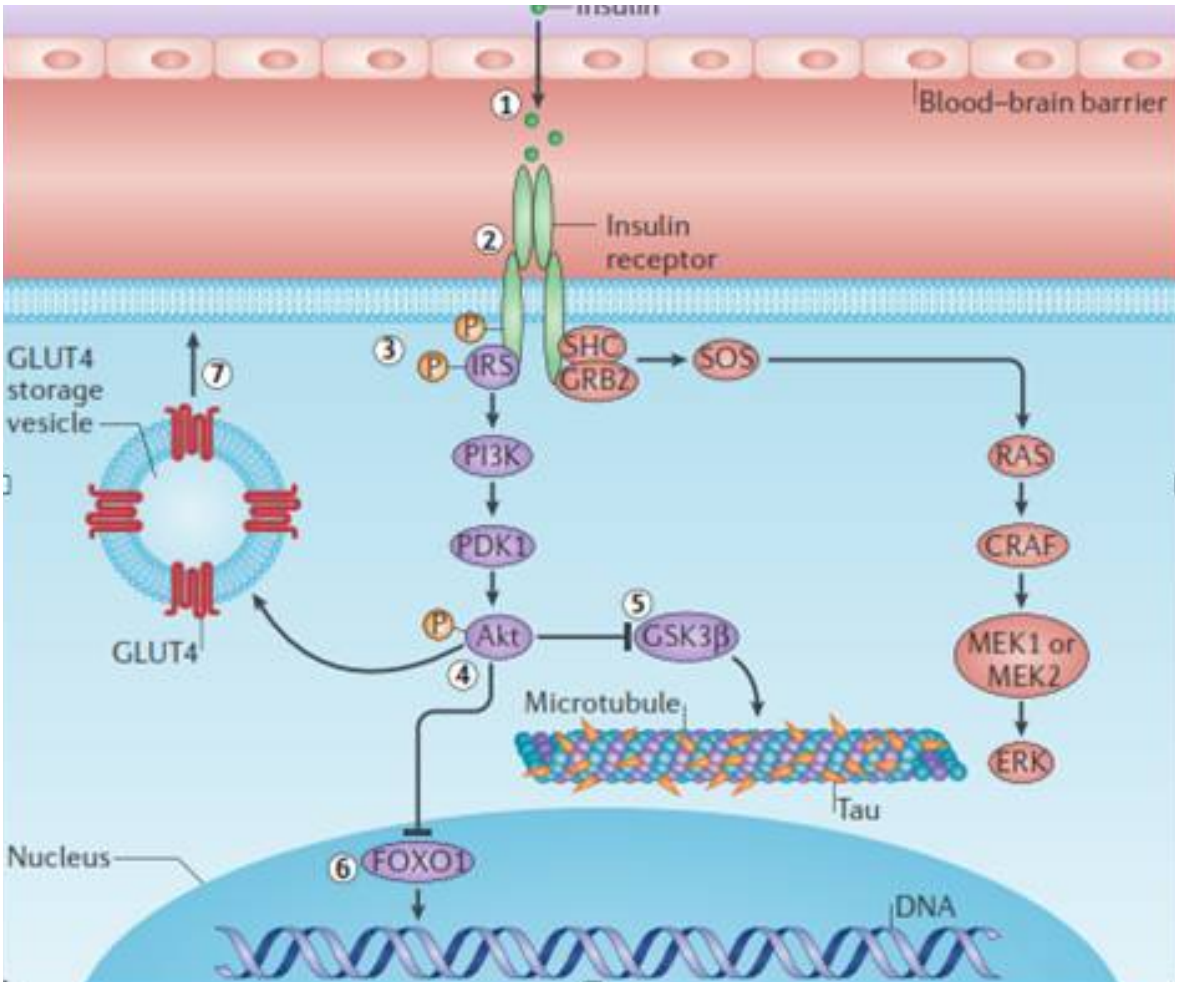

Figure 1. Insulin receptor signalling in the brain.[10]

clinical trial was conducted in 2018 to assess the association of SVI with cognitive function in T2DM. SVI was assessed by spectral analysis of HRV to calculate the ratio of low-frequency to high-frequency (LF-HF ratio) of HRV and cognitive function was assessed by recording the positive wave that appears in 300 milliseconds from application of stimulus in event-related potential tracing (P300). This study found that P300 latency was significantly prolonged in T2DM group compared with control group. LF-HF ratio of HRV was found to be correlated and linked with P300. It can be concluded that SVI could be the physiologic link to cognitive impairment in T2DM patients.[15]

THERAPEUTIC CHALLENGES

Intranasal insulin has emerged as a promising intervention for treatment of cognitive impairment in T2DM patients. Zhang et al.[23] conducted a randomized, double-blind, placebo-controlled study to evaluate the acute effects of intranasal insulin on resting-state brain functional connectivity in older adults with T2DM. After administrating a single 40 IU dose of intranasal insulin to 14 diabetic subjects and intranasal saline to 14 control subjects, resting-state functional connectivity between the hippocampal region and default mode network (DMN) was quantified using functional MRI (*f*MRI) at 3 Tesla. Following intranasal insulin administration, diabetic group demonstrated increased resting-state connectivity between the hippocampal regions and the medial frontal cortex (MFC) as compared with placebo. This trial proved that regulating memory with intranasal insulin use may modify functional connectivity among brain regions and complex cognitive behaviors. This trial also improved visuospatial memory and increased perfusion in the insular cortex compared with the control group. This acute improvements of cognitive function in T2DM patients may be related to vasodilatation in the anterior brain regions, such as insular cortex that regulates attention-related task performance.[24]

Future tasks of researchers include unravelling of the etiology of the brain complications of T2DM by integrating findings from different imaging modalities and detailed clinical phenotyping and by linking structural MRI abnormalities to histology. Understanding the underlying mechanisms is necessary to establish interventions that will improve long-term cognitive outcomes for T2DM patients.

CONCLUSION

The link between T2DM and cognitive impairment is still not well understood. Insulin resistance of the brain plays most important role of cognitive impairment in T2DM. Further studies investigating both markers associated with cognitive decline in T2DM and therapeutic interventions based on established linking pathophysiology are needed to achieve better outcomes in T2DM patients.

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Giant Recurrence Pituitary Adenoma After Three Times Transphenoidal Removal Surgery, One Craniotomy Procedure, and 30 Doses of External Radiotherapy

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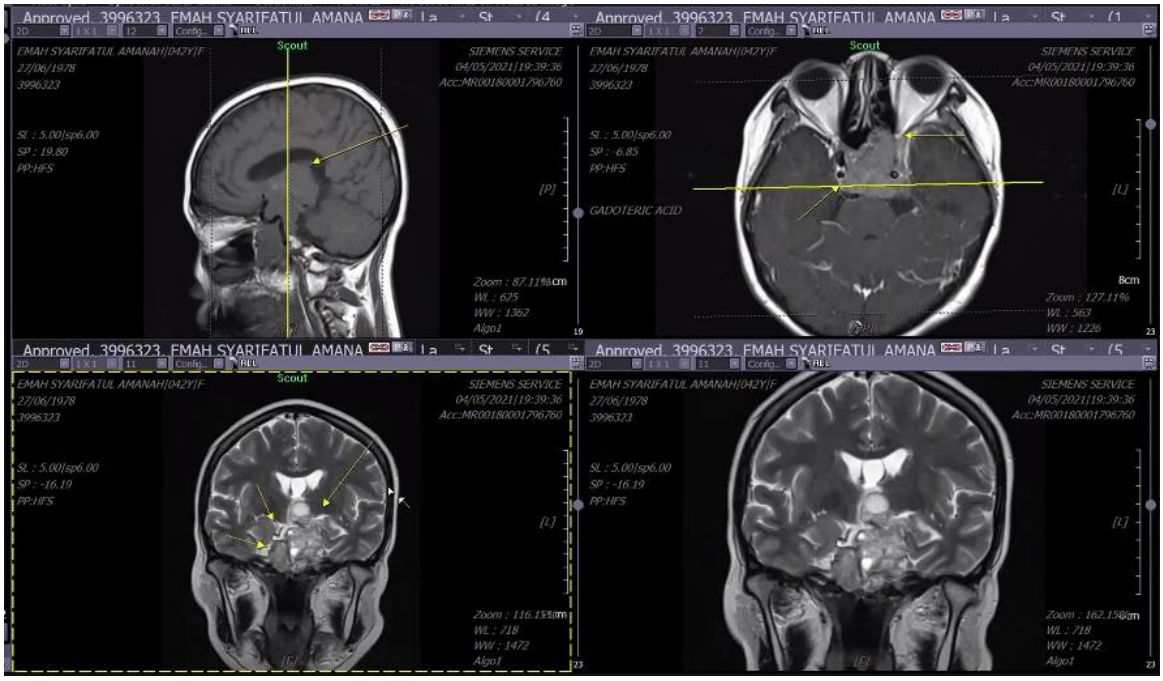

Figure 1. Dynamic pituitary MRI revealed giant recurrence pituitary adenoma after four times surgery and 30 doses of external radiotherapy.

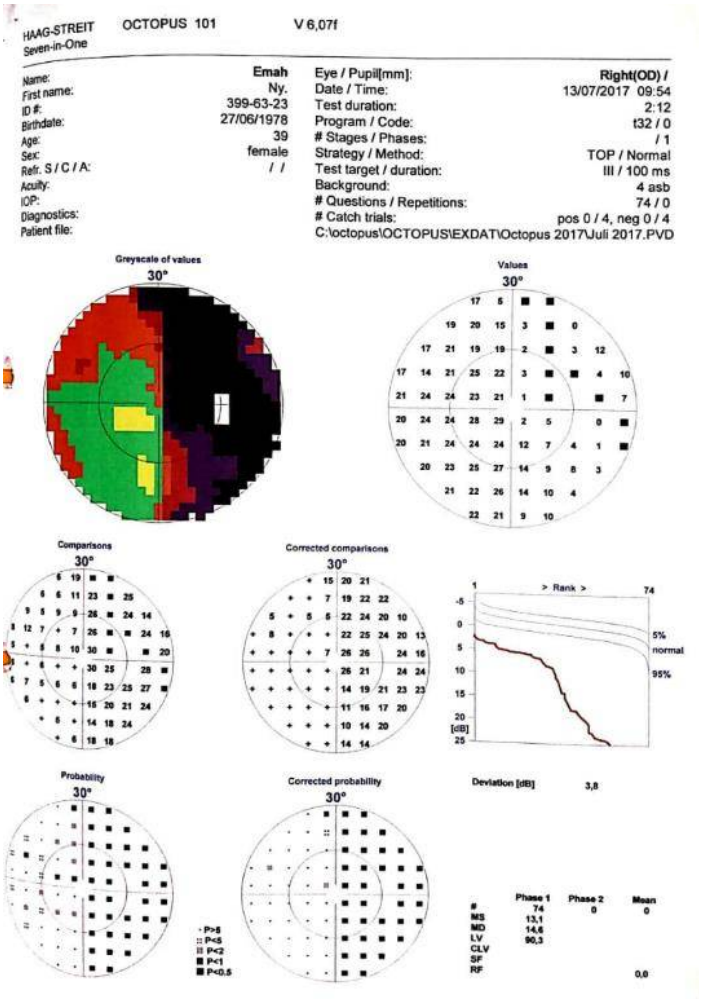

Figure 2. Campimetry assessment revealed bilateral temporal hemianopia.

This is a case of 42nd year-old woman with history of sight loss in her both eyes. She experienced headache and visual field decrease gradually since 2014. After several laboratory and imaging examinations, from her dynamic pituitary magnetic resonance imaging (MRI), it is concluded that she had a giant adenoma of the pituitary gland which compressed to her optic chiasm. From her pituitary laboratory hormone panel, it is revealed that the tumor is a non-functioning pituitary adenoma. From the neuro-ophthalmology (campimetry) examinations, she had papillae atrophy in her both eyes and also bilateral temporal hemianopia.

The patient underwent transphenoidal removal surgery in June 2016, followed by laboratory and imaging evaluations afterward. The surgery was repeated three times due to recurrence detected by headache and worsening visual field and imaging; in November 2006 and April 2017 (both transphenoidal removal surgery) and the last surgery was done in November 2019 with craniotomy removal surgery techniques. All of the histopathology of the pituitary gland is benign pituitary adenoma. Since the pituitary mass still reside and recur, pituitary team decided to radiate the recurrence pituitary adenoma with 30 doses of external beam radiotherapy (EBRT) at the department of oncology radiation in March 2020.

After 30 doses of external radiation, from the hormonal examinations, the morning cortisol serum was 0.9 mcg/dL (normal 3.7 – 19.4 mcg/dL) and Adrenocorticotrophic Hormone (ACTH) was < 0.1 pg/mL (normal 7.2 – 63.3 pg/mL), indicate that she had a secondary adrenal insufficiency. This condition was treated by substitution of oral steroid. Other pituitary

hormones i.e. Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating Hormone (TSH) were at the normal range.

Right now, the patient still complaining for her visual field loss, but no severe or extraordinary headache was perceived. Dynamic pituitary magnetic resonance imaging (MRI) 6 months and 1 year after external radiotherapy revealed that the size of the tumor is growing larger than before. Pituitary MRI explained there is a solid mass (size 6.4 x 6.3 x 4.2 cm) in axial and extra-axial of sella and parasella region, filled the sphenoidal sinus to left spatial and exert to surrounding intracranial structures. This condition is diagnosed with recurrence giant pituitary adenoma after four times surgery and optimal dose of external radiotherapy. It is a very rare, difficult, yet challenging case to resolve.

Prevalence of pituitary tumors is 80-100 cases per 100,000 with incidence 4 new cases in 100,000 each year. Generally, pituitary tumors are common and easily treated by surgery and medical treatments. But, a small subset of pituitary tumors is classified as aggressive based on resistance to medical treatment and multiple recurrences despite standard therapies such as surgery, pharmacology, and external radiotherapy.[1] At least 50% of surgically resected non-functioning pituitary adenomas will recur.[2] About 30% of patients will show tumor regrowth 0.4-37 years after surgery. The risk of progression is higher in the case of residual tumor and extrasella region.[1]

Our patient experienced recurrence detected by sign and symptom of worsening of her visual field and by the evaluation of imaging study (MRI) which done every 6 months after surgery. After four times of surgery (one of which by craniotomy procedure) and 30 doses of external radiotherapy, the tumor still regrowth in a not so long-time evaluation.

There are some options for recurrence and aggressive non-functioning pituitary adenoma, such as surgery revision, external radiotherapy, and medical treatments. Surgical revision is eventually needed in 30-50% of non-functioning pituitary adenomas after surgery.[3] However, this is not an option for our patient because we have done four removal surgeries before. External radiotherapy may look a good option since the efficacy is doubtless and late radiotherapy seems as effective as early treatment for local control.[3] But again, our patient has undergone 30 doses of radiotherapy last year. So, in our pituitary team meeting, panel experts suggest the patient will not undergo surgery and external radiotherapy anymore. Medical and palliative therapy is the treatment of choice at this point.

Clinical Practice Guidelines from European Society for Endocrinology (ESE) has published recommendations for medical treatments for aggressive and recurrence pituitary adenoma. They recommend the use of temozolomide as first line chemotherapy. The standard dose regimen is 150-200 mg/m^2 for 5 consecutive days every 28 days. First evaluation of treatment response must be done after 3 cycles.[1] If radiological progression is demonstrated, temozolomide treatment should be ceased. It has been suggested to examine MGMT status by immunohistochemistry by an expert neuropathologist. Low expression of MGMT content in immunohistochemistry correlate with more positive response to temozolomide.[4] However, a trial of temozolomide may be considered in patients with high MGMT expression. Combination of temozolomide and other chemotherapy drugs such as capecitabine, thalidomide, and bevacizumab is also being reported in case reports, but the efficacy is still need to study further.[1]

Another drug which can be used is cabergoline, a dopamine agonist usually used for treating prolactinoma. In difficult and recurrence pituitary tumors, cabergoline can be an option.[3] Recently, researcher have conducted a randomized clinical trial which showed cabergoline as an effective drug for treating residual non-functioning pituitary adenoma. Cabergoline shows 70% efficacy for shrinking non-functioning pituitary adenomas.[5] Since medical treatment was the only option for our patient at this point, we give cabergoline and plan to carry out immunohistochemistry (MGMT staining) for the patient as a requirement for our patient to get temozolomide from our national health insurance.

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Psychotherapy for Healthcare Provider During COVID-19 Pandemic: An Evidence Based Clinical Review

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ABSTRAK

Latar belakang: *tenaga kesehatan merupakan salah satu kelompok yang terdampak secara psikis maupun somatik dari pandemi COVID-19. Banyak dari tenaga kesehatan yang dilaporkan mengalami kecemasan, depresi, hingga insomnia. Studi ini bertujuan untuk mengidentifikasi psikoterapi sebagai intervensi kesehatan psikologis untuk tenaga kesehatan selama pandemi COVID 19.* ***Metode:*** *kajian klinis berbasis bukti terkait psikoterapi sebagai suatu intervensi kesehatan psikologis yang dilaporkan dalam literatur, dan dikembangkan untuk petugas kesehatan selama pandemi COVID-19. Kajian ini dilakukan mengikuti protokol kajian klinis berbasis bukti dengan mencari literatur digital menggunakan sumber data dari Pubmed, Proquest, Cochrane, dan Google Scholar.* ***Hasil:*** *terdapat 6 artikel untuk dilibatkan dalam tinjauan sistematis ini. Semua subjek yang masuk dalam penelitian ini adalah tenaga kesehatan. Keenam studi yang didapatkan merupakan studi observasional dan melakukan penliaian menggunakan kuesioner secara potong lintang. Strategi psikoterapi setiap penelitian berbeda-beda yaitu baik dengan psikoedukasi, dukungan social, hingga terapi musik. Secara keseluruhan menunjukkan bahwa psikoterapi dapat mengurangi kecemasan, depresi, dan insomnia.* ***Kesimpulan:*** *kondisi psikologis tenaga kesehatan perlu mendapatkan perhatian selama pandemic Covid-19. Meskipun belum ada standar terapinya, psikoterapi dapat menjadi pilihan karena terbukti mampu untuk mengurangi kecemasan, depresi, dan insomnia.*

Kata kunci: *psikoterapi, petugas kesehatan, COVID-19.*

ABSTRACT

Background: *health workers are one of the groups affected physically as well as psychologically from the pandemic. Recent studies showed many of the health workers reported experiencing anxiety, depression, and insomnia. This study aims to identify psychotherapy as a psychological health intervention, for healthcare workers during the COVID-19 pandemic.* ***Methods:*** *an evidence based clinical review of psychotherapy as a psychological health intervention, reported in the literature, which is developed for healthcare workers during*

the COVID-19 pandemic. The review was conducted following set out for Evidence-based clinical review by searching the following digital libraries: PubMed, ProQuest, Cochrane, and Google Scholar. ***Results:*** *six publications were selected. The identified psychotherapy used as a mental or psychological intervention for healthcare workers during COVID-19 consists of supportive psychotherapy, psychoeducation, social support, and music therapy. Overall, it shows that psychotherapy, especially supportive psychotherapy, can reduce anxiety, depression, and insomnia.* ***Conclusion:*** *the physiological condition of health workers needs to get attention during the COVID-19 pandemic. Although there is no standard of therapy yet, psychotherapy could be an option as it is proven to be able to reduce anxiety, depression, and insomnia.*

Keywords**:** *psychotherapy, healthcare worker, COVID-19.*

INTRODUCTION

After World Health Organization (WHO) declared COVID-19 as pandemic in March 2020, total cases reached 50 million cases in November 2020 with total daily new cases approximately 500 thousand cases. Indonesia ranks 21st in the world with total death of 14 thousand people.[1] COVID-19 pandemic is not only affecting physical but also psychological health and well-being.[2] In general population, this pandemic can lead to the development of new psychiatric symptoms or worsening the pre-existing illnesses.[3] Health care workers (HCW) are also prone to be physically and psychological affected. Many of HCW are reported to have high-rate symptoms of depression, anxiety, insomnia, and distress.[4] The prevalence rates of anxiety and depression among HCWs during COVID-19 are 23.2% and 22.8%, respectively.[5]

Long working hours, lack of personal protective equipment, and concern for their patients and their own families are only several precipitating factors contributing to psychological stress of HCW.[6,7] These psychological health problems not only affect HCWs' attention, understanding, and decision-making ability but could also affect their wellbeing.[8] Hence, protecting HCWs' psychological health is important to control the pandemic and their physical health. China's government has implemented several strategies to address these psychological problems by forming a psychological support team, establishing a shift system, and developing online platform to give education about transmission prevention among patients in hospital.[8]

HCWs need reassurance of their safety by receiving adequate personal protective equipment, support from colleagues and families, as well as appreciation from patients.[7,8] HCWs also need practice to control their emotions and reduce burn out. Psychological intervention for COVID-19 should be dynamic and flexible enough to adapt quickly to the different phases of the pandemic.[9] Therefore, this Evidence-based clinical review aims to identify strategies used of psychotherapy as psychological intervention to manage HCWs' psychological health during the COVID-19 pandemic.

METHODS

This article follows the quality reporting guidelines evidence-based clinical review to ensure clarity and transparency of review reporting.[10]

The search process started on October 11, 2020, by consulting the following sources: PubMed, ProQuest, Cochrane, and Google Scholar. The following search strings were applied to the titles, abstracts, and keywords of the articles for the automatic search of publications in the mentioned digital sources: - "psychotherapy" AND "healthcare workers" AND "COVID-19"- "psychotherapy" AND ("doctors' OR "nurses") AND "COVID-19". The inclusion criteria included clinical/intervention studies, observational and cross-sectional studies. All subjects were healthcare workers during COVID-19 pandemic. Full-text articles are in English or Indonesian translation with no limitation of publication time. A total of 6 studies were identified after application of inclusion criteria and eligibility criteria as presented in **Figure 1**.

RESULTS

Of the total studies identified, we obtained 637 articles, with details of 40 articles from the PubMed database, 0 articles from Cochrane, 77 articles from ProQuest, and 520 articles from Google Scholar. From the screening for articles duplications, we got a total of 240 articles, and after assessment based on inclusion and exclusion criteria, we got 26 articles.

Of these 26 articles, there are 12 articles of which we can get the availability of the full-text manuscript. Out of these 12 articles, a total of 6 studies were included in the evidence-based clinical review after the application of inclusion criteria and eligibility criteria. As presented, we have selected 6 articles to engage in this evidence-based clinical review. The flow chart of the literature searches and selection of studies is presented in **Figure 1**.

DISCUSSION

Some studies reported healthcare workers have experienced varying degrees of stress, anxiety, depression, and insomnia. Compared to non-medics, the effects of anxiety and depression during pandemics did not differ significantly. The difference is in the psychological stressors experienced.[15,16] Psychological disorders experienced by healthcare workers are caused by the speculation about transmission mode, speed of the infection spread, lack of treatment or vaccine protocols, lack of PPE, high workload such as treating rapidly worsening patients, unhealthy rotation of work shifts, and fear of spreading infections to nearby people.[3,17,18] Based on Cai et al.[6] research, younger healthcare

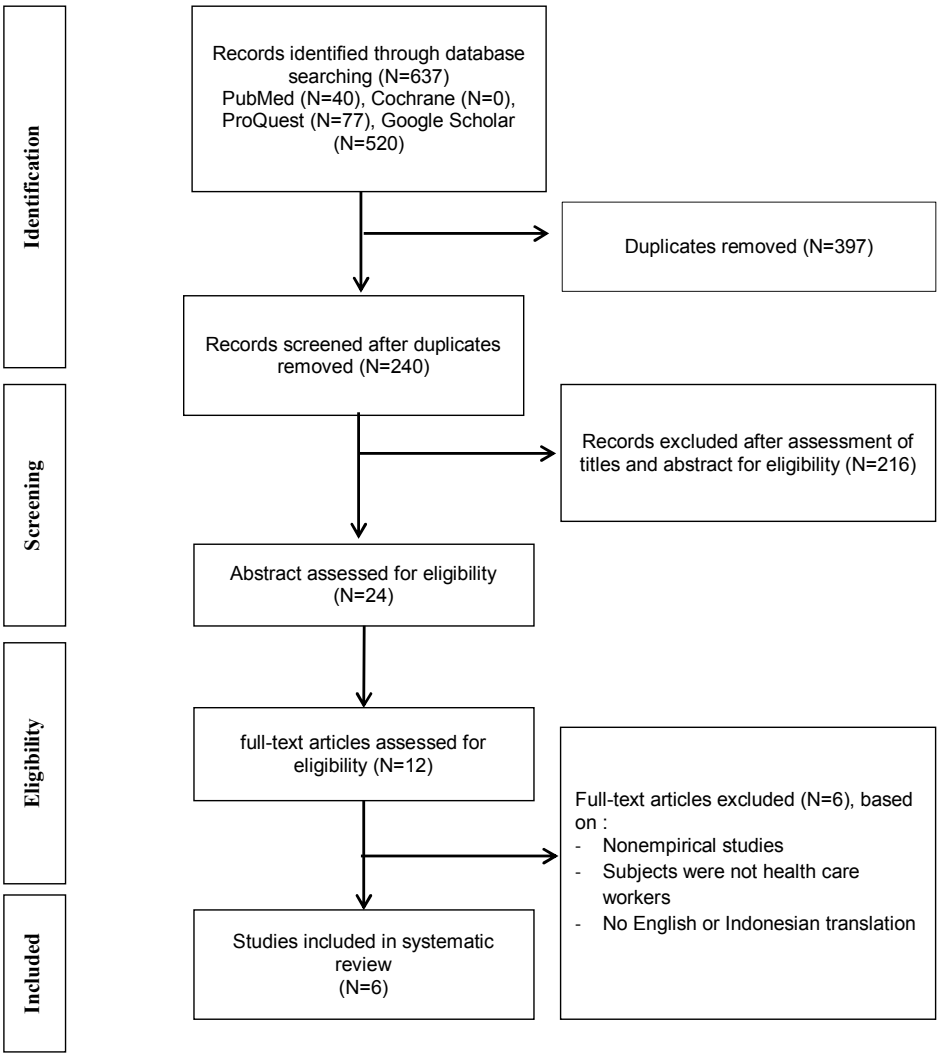

Figure 1. Flow chart of the literature search and selection of studies.

Table 1.

Author	Population and Criteria of Study	Design Study and Method	Intervention	Output	Outcome
Cai H, et al[6] (2020)	Population: 534 frontline healthcare workers during the COVID-19 outbreak. The participants included doctors and nurses from departments of infectious diseases, emergency medicine, fever clinics, and intensive care units, and included technicians from radiology and laboratory medicine, and hospital staff from the section of infection prevention throughout Hunan province between January and March 2020.	Design: cross sectional observational study. Method: Study questionnaire included five sections and 67 questions to evaluate psychological impact and coping strategies to prevent.	Follow strict protective measures, learn about COVID-19, its prevention and mechanism of transmission, social isolation and motivating to face the COVID-19 outbreak with positive attitude	Study questionnaire for evaluation on psychological impact, coping strategies and feedback response.	Personal coping strategies in the form of supportive psychotherapy, such as: telling the difficulties experienced with family and friends, talking and motivating yourself to face the pandemic that occurs by thinking positively gives a pretty good effect.
Ping, et al[11] (2020)	25 Hospital University Malaysia Sabah (HUMS) nurses who were working on the COVID-19 frontline in early February 2020.	Cross sectional study	UBPI (ultra-brief psychological interventions) handbook called UC-19, which incorporate multiple techniques from various evidence based psychological interventions, including cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), dialectical behavioral therapy (DBT), motivational interviewing (MI) and early intervention program (EIP).	Questionnaire contains responses experienced after the use of the handbook.	All participants report positive feedback on the techniques presented in the handbook.

Table 1.

Author	Population and Criteria of Study	Design Study and Method	Intervention	Output	Outcome
Blake, et al[12] (2020)	55 Healthcare workers, British nationals, recruited in 3 days in early March	Cross sectional study	Electronic learning package (e-digital) contains: introduction of psychological problems, how to communicate, coping strategies, social and family roles, as well as self-management and emotional control.	Questionnaire contains ease and satisfaction after the use of electronic learning guides on activities and psychological impacts experienced	82% of healthcare workers who reported using e-digital achieve satisfaction and will continue to use in the future.
Buselli, et al[13] (2020)	106 healthcare workers (79 female, 27 male)	Preliminary Study Method: Screening using questionnaire (BDI-II, STAI-Y1 and STAI-Y2), psychiatric and psychologic consultation, team briefing.	PsicoCovid19 (a team consist of occupational doctor, 3 psychologists, and 1 psychiatrist). Contact with hospital manager, monitoring hospital staff (symptoms, examination), psychoeducation (leaflet, visits), team briefing (case discussion), psychiatric monitoring, therapy	Beck Depression Index questionnaire (BDI), State-Trait Anxiety (STAI)-Y1 and STAI-Y2 questionnaire	Overall satisfaction with the PsicoCovid19 services.
Xiao, et al[14] (2020)	180 healthcare workers handling COVID-19 patients	Cross sectional study Methods: Measuring with Self-Rating Anxiety Scale (SAS), General Self-Efficacy Scale (GSES), Stanford Acute Stress Reaction (SASR) questionnaire, Pittsburgh Sleep Quality Index (PSQI), and Social Support Rate Scale (SSRS).	Social support (concern and support from other people), measure with social support rate scale (SSRS).	Self-Rating Anxiety Scale (SAS), General Self-Efficacy Scale (GSES), Stanford Acute Stress Reaction (SASR) questionnaire, Pittsburgh Sleep Quality Index (PSQI), and Social Support Rate Scale (SSRS).	Social support didn't influence sleep quality directly, but can reduced stress and anxiety, and improving self-efficacy.
Giordano, et al[15] (2020)	34 healthcare workers (14 doctors, and 20 nurses) work in COVID-19 unit.	Preliminary study Methods: Participant fill self-assessment questionnaire before and after listening music therapy. Music therapy prepared for relaxation, reduce stress and anxiety, and improving concentration. Interview for evaluation occurs once in a week. Playlist modified based on weekly interview	Music therapy listened from a headphone for 15-20 minutes, repeated until four weeks. healthcare workers were let free to decide when and how to listen to their music therapy during the weeks	Questionnaire	Questionnaire result shows that musical therapy significantly reducing stress and anxiety, improving emotional status. So as the result of modified musical therapy.

workers are more worried about infecting their families while older healthcare workers are also concerned about their own health.

There are currently several studies that report psychological interventions for healthcare workers, but not many have reported their effectiveness. In making interventions for healthcare workers, it should be known what protective factors can neutralise negative impacts during and after the pandemic. One of the most commonly reported protective factors is having social support.[17]

The results of the literature search showed that supportive psychotherapy is good for every setting, including emergency setting and enhancing the coping mechanism. There are some psychological interventions that are quite popular among healthcare workers. Healthcare workers are more comfortable with social support from family and work mates than from professional help.[3] Some of the things, colleagues can do are to start seeing signs of psychological disorders in their co-workers, such as having nightmares, difficulty sleeping, not being able to stop worrying, being restless, being irritable, and unexplained medical symptoms starting to appear. Other ways to do this are to give them the opportunity to talk, to show usable resources, to be good co-workers, to be consistent, to provide peace of mind, to support them to keep taking care of themselves, and to help them to explore the causes of stress.[18]

The role of individuals themselves is very important in the success of the psychological interventions, with coping strategies, such as increasing self-knowledge about COVID-19, using PPE properly, instilling positive values, making the most of rest time, music therapy, and watching TV.[6] Utilisation of electronic media in the form of digital learning packages, applications, and social media can be one of the efforts to reduce psychological disorders in healthcare workers. Some countries that have implemented this include Malaysia, the United Kingdom, the U.S., and Saudi Arabia.[11]

Research of music therapy by Giordano et al.[15] provides effective results in lowering the intensity of fatigue, sadness, fear, and worry. It is explained by the importance of the psychobiological effects of music on stressful conditions which will decrease hypothalamus-pituitary-and adrenal axis action activity, resulting in the decrease of cortisol production.[19-24] This music therapy may also be applicable to units working in high stress conditions such as those involved in surgical procedures. In the end, such supportive psychotherapy enhances emotional state and improves the endocrine function, through lymbic system and psycho-neuro-immuno-endocrine mechanism. [25-29]

Psychological intervention should also involve the role of organisations (in this case hospitals and governments) as policymakers and providers of facilities.[13] Working hours, night shifts and workload are factors that determine the well-being of healthcare workers. Several things' organisations can do to support their medical staff include providing access to counselling to psychosomatics and psychiatrists, providing accommodation for self-isolation to alleviate the concerns medical personnel that could infect their families, and providing guidance during self-isolation.[18]

According to Widjaja, et al,[30] to protect healthcare workers during the COVID-19 pandemic requires approaches from various aspects, biological, psychological, and social aspects. Psychological disorders are associated with decreased immune systems. Therefore, it is important to make psychological interventions for healthcare workers.

Shatri, et al.[31] stated that COVID-19 affects people in the community, including healthcare providers, as well as those who are in quarantine and people being released from quarantines. Healthcare providers in the middle of the pandemic may experience stigma and fear-associated discrimination from others in their community. To overcome such situation, firstly, we have to stay healthy physically and maintain positive energy to live a fulfilling life of becoming truly healthy people.

In the context of crises or pandemics, Psychological First Aid (PFA), especially supportive psychotherapy, becomes the basic approach clinicians can use when responding to crises. This approach is based on Maslow's hierarchy of needs in which physical needs and

safety are addressed before moving to emotional stabilisation.[32] The term Psychological First Aid (PFA) itself has been coined to capitalise on the analogy between bodily and psychological injuries. The main idea is that people without extensive medical knowledge or training can be taught to provide immediate help without further injuring a person.[32,33] As with crisis intervention, the key ingredients of PFA are empathy and compassion, and the imperatives are to reduce the risk of harm, stabilise psychological distress, and provide practical assistance, such as connecting the person with other resources. [33,34]

Supportive psychotherapy does not aim to change personality traits or defence mechanism, but rather to stabilise them. It has a specific meaning derived from psychoanalysis, which describes the therapist's support for the patient's adaptive or more mature personality defence. Accordingly, it can be used in otherwise well-adjusted persons experiencing stressful situations, which results in tension and distress, but it can also be used for clients who are not suitable for other more sophisticated forms of therapies. It can be used in any disorders, any age groups, and every setting including emergency and mass disaster setting [32,35,36]

Therefore, mental health of professionals including healthcare providers following a pandemic can expose them to burnout syndrome of caregivers. In a disaster, it can be experienced by not only healthcare workers but also other professionals such as policemen, fire fighters, and volunteers who come in contact with painful experiences. Nobody is prepared or immune to this devastating effect. In addition, we need to consider fatigue of mental status in healthcare workers. The basic intervention consists of debriefing, identifying critical incidents, helping set the situation in perspective, and reinforcing the capacity and skills of the healthcare workers. In this setting, supportive psychotherapy is very useful to control tension in their mental state. [35,37]

CONCLUSION

COVID-19 pandemic's impact in healthcare workers affects not only physically but also psychologically and socially. Psychological intervention is needed, such as doing psychotherapy, especially supportive psychotherapy, which is proved to be effective to encounter that condition in almost every setting. Families, colleagues, professional organisations, and government involvement also support successful efforts and safety for healthcare workers. Advancement in medical science, psychology, and technology have provided a newly form of psychological intervention, such as electronic media (e-book, e-package, digital learning), social media, and digital application. Furthermore, we expect more studies which learn about the effectiveness of psychological intervention for healthcare workers during COVID-19 pandemic.

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The Management of Pulmonary Fibrosis in COVID-19

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ABSTRAK

Fibrosis paru pasca infeksi COVID-19 dapat terjadi akibat komplikasi ARDS yang ditandai dengan adanya kegagalan re-epitelisasi alveolar, aktifasi fibroblast, akumulasi kolagen dan matriks ekstraseluler lain secara berlebihan sehingga menyebabkan kelainan arsitektur paru. Ada beberapa faktor risiko untuk terjadinya fibrosis paru pasca-COVID yaitu usia lanjut, riwayat ARDS, penggunaan ventilator mekanik yang dapat menyebabkan terjadinya injury paru, riwayat merokok dan konsumsi alkohol. Diagnosis fibrosis paru pasca-COVID ditegakkan berdasarkan gejala klinis dan gambaran karakteristik kelainan CT scan paru. Hingga saat ini belum ada terapi definitif untuk fibrosis paru pasca-COVID, namun beberapa obat antifibrosis dapat dipertimbangkan untuk diberikan. Selain terapi medika mentosa, rehabilitasi paru dan terapi oksigen jangka panjang juga harus merupakan bagian dalam tatalaksana komprehensif fibrosis paru pasca-COVID-19.

***Kata kunci**: fibrosis paru, COVID-19.*

ABSTRACT

Pulmonary fibrosis due to COVID-19 is recognized as sequel of ARDS characterized by failed alveolar re-epithelization, fibroblast activation, excessive collagen deposition and other extracellular matrix components that disrupt the normal lung architecture. There are risk factor for pulmonary fibrosis namely advanced age, severe ARDS infection, mechanical ventilation due to ventilator-induced lung injury, smoking and chronic alcoholism. Diagnosis of post-COVID pulmonary fibrosis can be made by clinical symptoms and characteristic finding from lung CT scan. To date, there is no definitive treatment for post-inflammatory pulmonary fibrosis after COVID-19 infection, however some of antifibrotic therapies may be considered. Beside medical treatment, pulmonary rehabilitation program and long-term oxygen treatment should be included as part of comprehensive treatment for pulmonary fibrosis due to COVID-19.

Keywords*: *pulmonary fibrosis, COVID-19.

INTRODUCTION

The novel coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has generated huge concern for high mortality and lack of specific and effective treatment. The most critically ill patients in the context of SARS-CoV-2 infection may develop acute respiratory distress syndrome (ARDS). It has been found that 40% of patients with COVID-19 develop ARDS, and 20% of ARDS cases are severe.[1] Pulmonary fibrosis is recognised as sequel of ARDS characterized by failed alveolar re-epithelization, fibroblast activation, excessive

collagen deposition and other extracellular matrix (ECM) components that disrupt the normal lung architecture. Excessive depotition of ECM is therefore central to the process of lung fibrosis. It manifests as an irregular interlobar septal thickening and reticular pattern with traction bronchiectasis on chest CT scan.[2] The prevalence of post-COVID 19 fibrosis will become apparent with time, but early analysis from patients with COVID-19 on hospital discharge suggest that more than a third of recovered patients develop fibrotic abnormalities. A study of Italian COVID-19 pandemic survivors found that as many as 45% patients still complained of dyspnea at follow up visit conducted a mean of 60 days after the initial onset of the symptom. A follow-up study by Zhao et al.[3] of pulmonary function and radiology in 55 COVID-19 survivors 3 months after recovery showed that 71% had residual CT abnormalities, including evidence of interstitial thickening in 27%. Abnormal lung function has also been identified at the time of discharge from the hospital and after 2 weeks later in up to 47% cases. Restrictive ventilatory defects is the most common abnormality of lung function seen in about 25% of cases. The pulmonary function abnormalities being worse in those with severe acute infection.

Follow up of cohorts of post-COVID survivors are already underway at several centers to determine weather fibrosis changes on CT scan are persist or gradually improved or even worsen with the passage of time. This has implications not only for patient prognosis but also for treatment. Antifibrotic may have an important role in patients with progressive lung fibrosis **(Figure 1)**.[3]

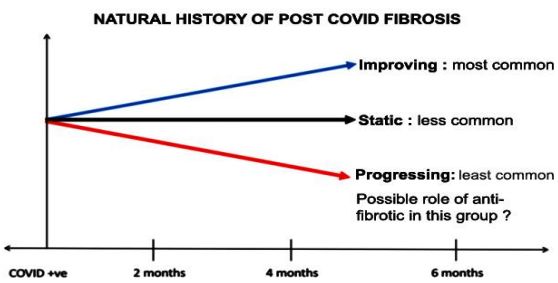

Figure 1. The natural history of post-COVID pulmonary fibrosis will be one of three possible course.

Compared with the last CT scan before discharge, the abnormalities (including focal/multiple GGO, consolidation, interlobular septal thickening, subpleural lines and irregular lines) in lung are gradually absorbed in the first and second follow-ups after discharge. The lung lesion of 64.7% discharged patients were fully absorbed after 4-week follow-up. It indicates reversible lung tissue damage of COVID-19 cases. It also suggest that the prognosis of non-severe patients is favourable, and clinical intervention should be conducted to prevent the worsening of COVID-19 patients.[1]

RISK FACTORS FOR PULMONARY FIBROSIS IN SARS-COV-2

The factors mediating a profibrotic response to SARS-CoV-2 virus are not fully known, but from some studies suggest that age, severity of illness, use of mechanical ventilation, smoking and chronic alcoholism may contribute.[2,4]

Age. Pulmonary fibrosis is reported more often in patients with advance age. The median age for diagnosis is 65 years, and it rarely occurs before 50 years. In a follow-up study, advance age correlated with the risk of developing pulmonary fibrosis at 6 months after discharge. The exact reason for this association is unknown; however, older patient are more susceptible to both SARS and MERS similar to SARS-CoV-2 infection and more likely to have severe symptoms.[2,4]

Illness Severity. According to World Health Organization, 80% of SARS-CoV-2 infection are mild, 14% develop severe symptoms, and 6% will become critically ill. Factors associated with increased diseases severity include comorbidities such as hypertension, diabetes and coronary artery disease. Laboratory findings of lymphopenia and elevated lactate dehydrogenase (LDH) correlate with increased disease severity. Serum LDH level has been used as marker of disease severity following acute lung injury. It is an indicator of pulmonary tissue destruction and correlate with the risk of mortality. The extent of lung injury and inflammatory respons correlate with the extent of fibroblastic response required to repair the injury. Peaked LDH level was found to significantly correlate with the risk of pulmonary fibrosis following MERS-

CoV infection. Similarly, a follow-up study at 6 months after discharge in SARS patients show a significant relation between elevated levels of LDH during acute illness and an increased risk of developing pulmonary fibrosis.[2]

Length of ICU stay and Mechanical Ventilation. ICU care is required in 5-12% of COVID-19 patients, with the criteria for ICU admission varying from one region to another. While disease severity is closely related to the length of ICU stay, mechanical ventilation poses an additional risk of ventilator-induced lung injury (VILI). Ventilator-induced lung injury is an acute lung injury arising from or exacerbated by mechanical ventilation. Abnormalities of pressure or volume setting underlie this injury leading to release of proinflamatory mediators, worsening acute lung injury and increased mortality or pulmonary fibrosis in survivors. In a follow-up study of 27 patients who had mechanical ventilation for ARDS, 110-267 days after extubation, 23 patients (85%) had pulmonary fibrosis with a significant relationship to the duration of pressure-controlled inverse-ratio ventilation.[2]

Smoking. Smoking has been linked to the pathogenesis of various lung disease such as emphysema, chronic bronchitis and pulmonary fibrosis. Smoking is associated with chronic oxidative stress, increased expression of inflammatory cytokine and interstitial lung fibrosis. The injury associated with smoking continues even after cessation. A systemic review shows that smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to need ICU admission and mechanical ventilation or die compared to nonsmokers.[2]

Chronic Alcoholism. Chronic alcoholism has been cited a predisposing factor for severe respiratory infection. Alcohol abuse is associated with recurrent pneumonia due to gastric aspiration. There is also evidence of additional injury to the lung in chronic alcoholism. Chronic alcoholism may cause glutathione depletion, chronic oxidative stress, inflammation and induction of TGF-? in the lung, thereby increasing the risk of acute lung injury and pulmonary fibrosis.[2]

PATHOGENESIS

Although ARDS seems to be the main predictor of pulmonary fibrosis in COVID-19, several studies showed that COVID induced ARDS is different from the classical ARDS. Result from CT scan finding in many cases are also not suggestive of classical ARDS. Therefore mechanism of pulmonary fibrosis in COVID-19 is different from that of idiopathic pulmonary fibrosis (IPF), especially with pathological findings pointing to alveolar epithelial cells being the site of injury and not the endothelial cells.[1] Based on pathological pattern of pulmonary fibrosis, the clinical process of COVID-19 patients can be divided into three stages **(Figure 2)**.[5] The first stage: the SARS-CoV-2 has just invaded the upper respiratory tract. Patients

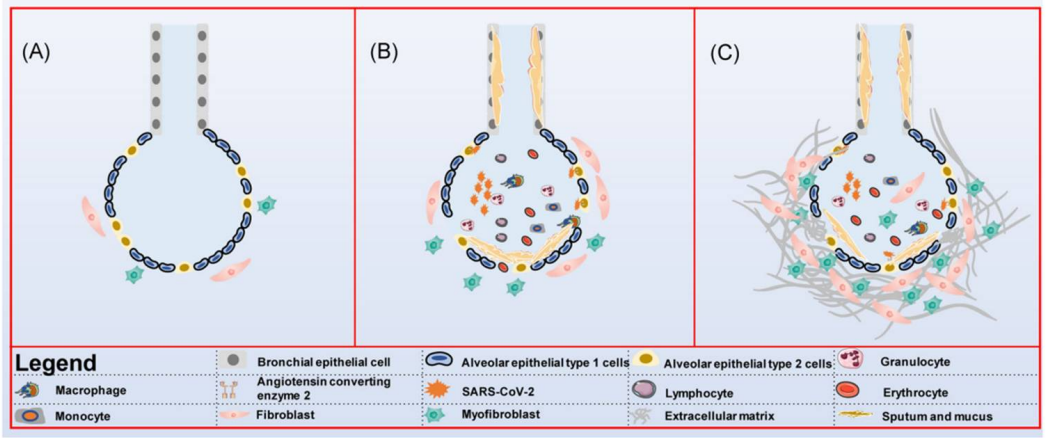

Figure 2. Pathological pattern of pulmonary fibrosis caused by COVID-19.

often have only cough, fatique and sore throat. From the imaging there is no manifestation of pneumonia. If the patient's immunity are strong enough at this time, it can be self-limited. The second stages: the stages of acute inflammatory reaction. Patients usually have fever, obvious respiratory tract symptoms (shortness of breath, dyspnea) and other symptom such as diarrhea. At this stage there are large number of inflammatory cells infiltrated in the lung and pneumonia could be seen in pulmonary tomography imaging. There is also a small number of fibroblast and myofibroblasts proliferate to repair damages alveolar epithelial cells (mainly type II alveolar epithelial cells). The third stage: the late stage of inflammation or recovery stage. With the improvement of the disease, pulmonary inflammation gradually decreased. However, due to the necrosis and shedding of abundant alveolar epithelial cells in previous stage, the human body initiate damage repair mechanisms through myofibroblast proliferation and extracellular matrix aggregation and finally the pulmonary fibrosis will occur. It is worth noted that the second and third stages often have no strict boundaries, and often develop simultaneously.[5]

The mechanisms by which SARS-CoV-2 infection cause pulmonary fibrosis are not fully understood. Most of study suggest that cytokine (espescially Transforming Growth Factor-β/ TGB-β), fibroblast, angiotensin converting enzyme 2, ventilator induced-lung injury (VILI) and oxygen toxicity have an important role for developing of pulmonary fibrosis in COVID-19 **(Figure 3)**.[2,6]

Cytokine and fibroblast. The alveolar wall has three components: the alveolar epithelium with its basement membrane, capillary endothelium with a basement membrane and an interstitium containing fibroblast, collagen fibrils, elastic fiber and macrophages. Pulmonary fibrosis usually occurs as a consequence of severe assault of the lung that cause alveolar wall injury. It occur as a result of dysregulation in one or more of the phases of wound healing: injury, inflammation and repair. SARS-CoV-2 can be act as inciting factor for alveolar wall injury. Fibroblasts as the effector cells in fibroproliferation are found in the alveolar interstitium. Following alveolar injury, fibroblast migration to site of injury is stimulated by fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), TGF-β and chemokines. Fibroblast proliferate and differentiate in to myofibroblast under the influence of vascular endothelial growth factor (VEGF), PDGF, TGF-β and IL-1. Fibroblast synthesize collagen, fibronectin and extracellular matrix (ECM) ground substance. In addition, mediators of repair process such as VEGF and TGF-β are secreted by myofibroblast. Myofibroblast produce denser but more disorganized ECM than fibroblast and persist longer at the site of injury. Tansforming growth factor-β is multifunctional cytokine playing a key role in the process of tissue repair following injury. Importance source of TGF-β including granule of platelets and macrophage. Transforming growth factor-β is

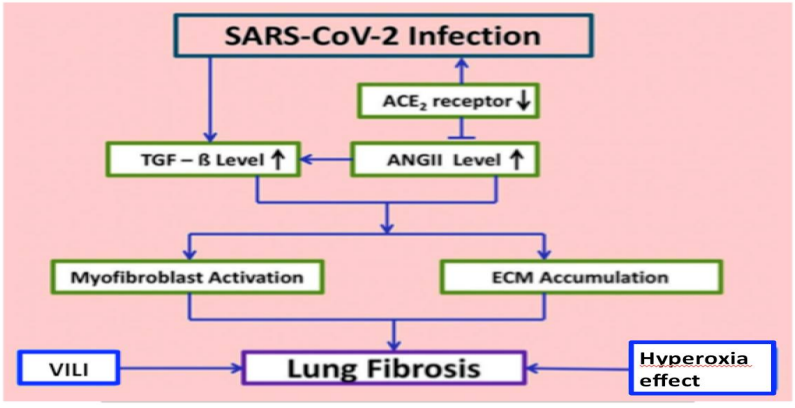

Figure 3. Postulated mechanism of SARS-CoV2 induced pulmonary fibrosis stressing the pivotal role of Angiotensin 2.

predominantly expressesd in the pathogenesis of pulmonary fibrosis because it stimulates extracellular matrix formation namely collagen, fibronectin, elastic fibres and ground substance. Transforming growth factor-β has fibrogenic potential by stimulating fibroblast migration and proliferation, inducing collagen and fibronectin deposition and inhibiting ECM degradation by matrix metalloproteinases. The stimulation of ECM deposition and inhibition of breakdown is fundamental to excessive accumulation of scar tissue in fibrosis. Platelet-derived growth factor are potent stimuli for migration and proliferation of fibroblast and has been reported as one of growth factors playing a key role in pulmonary fibrosis.[2,6]

Angiotensin Converting Enzime-2. Moleculer basis of progression to pulmonary fibrosis in COVID-19 is still unclear, but is believed to be multifactorial. The role of renin-angiotensin system has also been looked at with great interest as the high-affinity binding between the SARS-CoV-2 viral spike protein and the angiotensin-converting enzyme-2 (ACE2) receptor. Interaction between SARS-CoV-2 and ACE2 receptor has been shown to down regulate the level of the ACE2 receptor. Angiotensin-converting enzyme-2 have protective role in lung fibrosis. The decreased ACE-2 expression in turn leads to high angiotensin 2 (ANG II) level. ANG II is a potent vasoconstrictive peptide directly involved in development of inflammation and fibrosis. In addition to its role in regulating blood pressure, ANG II plays a pivotal role in fibrotic process signaling cellular and molecular events that lead to the development of abberant wound healing and pulmonary fibrosis. These include production of pro-inflamatory cytokines such as IL-6 and IL-8, production of reactive oxygen species among infected alveolar cells and activation of TGF-β which in turn leads to proliferation, migration and differentiation of fibroblasts to myofibroblasts with resultant deposition of collagen and fibronectin.[2,6]

Oxygen toxicity and VILI. The role two iatrogenic factors potentially contributing to the fibrosis encountered in survivor of severe COVID-19 pneumonia are oxygen toxicity and ventilator induced lung injury (VILI). Patients who develop post-COVID lung fibrosis are invariably those who are more sick with extensive, bilateral lung involvement, hence are more likely to required high oxygen concentration. High oxygen concentration on the other side; may result in heightened production of oxygen-derived free radicals which can damage the pulmonary epithelium. The sickest patients with ARDS from COVI-19 pneumonia are also more likely to require prolonged mechanical ventilation, often with generation of high plateau pressures in attempts to ventilate the stiff, noncompliant lungs. The role of mechanical stress as an inciting factor for lung injury is also well recognized and it is likely that VILI may also contribute to the pulmonary fibrosis.[2,6]

CLINICAL MANIFESTATIONS

Pulmonary fibrosis presents with the following symptoms : dry cough, fatique and dyspnea. Furthermore physical condition of the patients may deteriorates, accompanied by reducing of their body weight. Therefore, the quality of life patients suffering from this disorder are systematically regresses.[6] Knowledge of the natural evolution of lung abnormalities in COVID-19 may help the clinician to determine the stage of disease and indistinguishing them from potential complications when evaluating chest CT examinations. Roughly four stages of COVID-19 at chest CT scan have been described : (a) Early stage (0-5 days after symptom onset), which characterized by either normal findings or mainly ground-glass opacities; (b) Progresive stage (5-8 days after symptom onset), which is characterized by increased ground-glass opacities and crazy-paving appearance;(c) Peak stage (9-13 days after symptom onset) which is characterized by progressive consolidation and (d) late stage (?14 days after symptom onset), which is characterized by a gradual decrease of consolidation and ground-glass opacities, while signs of pulmonary fibrosis may appear. Pulmonary fibrosis signs consisting of parenchymal bands, architectural distorsion and traction bronchiectasis **(Figure 4)**. It should be noted that the temporal evolution and extend of lung abnormalities are heterogenous among different patients, dependent on the severity of

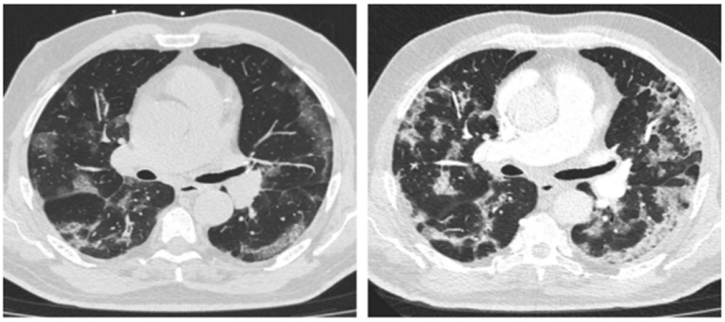

Figure 4. Natural evolution from ground-glass opacities to multifocal organizing consolidation.

the disease.[7]

Previous studies highlight that duration of disease is an important determinant for developing of post-ARDS pulmonary fibrosis. This study showed that 4% of patients with a disease duration of less than 1 week, 24% of patients with a disease duration of between weeks 1 and 3, and 61% of patients with a disease duration of greater than 3 weeks, developed fibrosis.[1]

DIAGNOSIS

The diagnosis of pulmonary fibrosis requires integration of clinical symptoms and radiologic information and history of severe ARDS due to COVID-19. Clinical symptoms of pulmonary fibrosis consisting of dry cough, fatique and dyspnea.[6] Lung CT scan finding from pulmonary fibrosis consisting of parenchymal bands, architectural distorsion and traction bronchiectasis.[7] Although there is no specific finding from laboratory testing, TGF-β and VEGF may increase as a marker of pulmonary fibrosis.

MANAGEMENT

Until now there is no specific therapy to handle post-inflammatory pulmonary fibrosis due to COVID-19 infection. Several studies are on going to determine an effective treatment for this chronic complication. While ARDS seems to be the main cause of pulmonary fibrosis in COVID-19, the pathogenesis of ARDS caused by SARS-CoV-2 is different from the typical ARDS. Some therapies may be considered for reducing the fibrosis process in lung after COVI-19 infection namely pirfenidone, nintedanib and mesenchymal stem cells.[8,-11.] Based on WHO guideline for clinical management of COVID-19, treatment with antifibrotic agent should be in context of clinical trial. Therefore for the legal aspect, outside of clinical trial all of these antifibrotic drugs should be given as investigational therapeutics based on the following criteria : no proven effective treatment exist, preliminary data from serial cases reports support the efficacy and safety of these drugs, treatments has been suggested by qualified scientific advisory committee on the basis of a favourable risk-benefit analysis, appropriately qualified ethich committee have approved such use, the patients informed consent is obtained and the results are documented and shared in timely manner with the wider medical and scientific community.[12]

Pirfenidone. Pirfenidone is a pyridone that is 2-pyridone substituted at positions 1 and 5 by phenyl and methyl groups respectively. Pirfenidone has both antifibrotic and anti-inflamatory properties and is able to mitigate the proliferation of fibroblast and production of protein and cytokines associated with fibrosis. It also mitigates the accumulation of extracellular matrix in response to cytokine growth factors such as TGF-β and PDGF. Pirfenidone can be administered as a monotherapy or combined with anti-inflammatory drug, IL-1 or IL-6 inhibitor which will exhibit a synergy effect in reducing its complication. The efficacy of pirfenidone has yet to be determined. Pirfenidone is given according to the principle of gradual increase in drug dose. The first week of treatment is 267

mg three times daily; second week of treatment is 534 mg three times daily, the third week and after is 801 mg three times daily (taking it with meal). Pirfenidone is given for 4 weeks or more, depent on the clinical respons. Pirfenidone can be associated with hepatotoxicity, whereas liver dysfunction is common in patients infected with SARS-CoV-2. Evaluation of liver and kidney function is necessary especially in patients with risk of liver and kidney damage (glomerular filtration rate of less than 30 mL/min per 1·73 m^2).[8-11]

Nintedanib. Nintedanib act as tyrosine kinase inhibitor that works on the receptors for FGF, PDGF, VEGF and on non-receptor kinases results in a broad inhibitory activity on the downstream signalling cascades of fibroblasts and myofibroblasts and potentially also on cells involved in angiogenesis in the lung. Dose for nintedanib is 150 mg twice daily for 12 months, in addition to standard of care. Similar to pirfenidone, it should be taken with food. Nintedanib also relates to liver and kidney damage, therefore closely monitored for these organ function should be performed. If necessary the dose of nintedanib can be reduced to 100 mg twice daily to prevent occurring of the liver and kidney injury.[7,9]

Mesenchymal stem cells (MSCs). Stem cells are the cells with a specific function with the ability of self-renewal, possess varied potency and differentiate into multilineages. Stem cell therapy has proven itself to be one of the most promising therapeutic approaches that provide opportunities to treat several diseases that were considered incurable like in post-COVID-19 pulmonary fibrosis. Mesenchymal stem cell therapy is preferred over other therapeutic strategies because they are free of ethical and social issues, they have a high proliferation rate and a low invasive nature. Mesenchymal cells are harvested from various sources, including adipose tissues, dental pulp, bone marrow, umbilical cord, fetal liver, various adult tissues (such as the infrapatellar fat pad, abdominal fat pad) and tissues associated with neonates (placenta, Wharton's jelly, cord blood, and amniotic fluid)).[13-19]

Infection of COVID-19 triggers an exaggerated immune reaction in the body by producing large amounts of various inflammatory factors including several cytokines, chemokines and immune reactive cells. The MSCs therapy might prevent the triggering of cytokine storm by the activated immune system, and the reparative properties of the stem cells might promote endogenous repair. Mesenchymal stem cells when intravenously injected will lead to some part of the population getting entrapped in the lungs. The pulmonary micro-environment could be recovered with the help of these MSCs, thus protecting the alveolar epithelial cells. Hence, pulmonary fibrosis of the lungs could be prevented, which may lead to curing COVID-19 caused pneumonia. In the multiple disease condition, the immunomodulatory effects will be responsible for improved function after MSCs infusion. A variety of paracrine factors are secreted by these cells. These paracrine factors interact with the immune cells, eventually leading to immunomodulation. The vigorous anti-inflammatory activities of MSCs will actually be responsible for improvements after their infusion in COVID-19 patients.[11-19]

In the Guidelines for Quality Control and Preclinical Study of Stem Cell Preparations (Trial), indications for stem cell therapy in COVID-19 include severe or critical illness from COVID-19-related pneumonia. Mesenchymal stem cells can be given via intravenous injection or intravenous cell infusion with dosage 1×10^6 cells/kg. The dose can be repeated for 3 times with 5 days interval. Intravenous injection of MSCs may produce a first-order lung effect, which leads to significant cell retention in the lungs, thus providing an advantage for lung tissue repair in COVID-19.[14, 16]

RESPIRATORY SUPPORT

Breathing Exercise. About 80% of the work of breathing is done by the diaphragm. After illness or general deconditioning, the breathing pattern may be altered, with reduced diaphragmatic movement and greater use of neck and shoulder accessory muscles. This results in shallow breathing, increasing fatigue and breathlessness, and higher energy expenditure. The "breathing control" technique is aimed at

normalizing breathing patterns and increasing the efficiency of the respiratory muscles (including the diaphragm) resulting in less energy expenditure, less airway irritation, reduced fatigue and improvement in breathlessness. The patient should sit in a supported position and breathe in and out slowly, preferably in through the nose and out through the mouth, while relaxing the chest and shoulders and allowing the tummy to rise. They should aim for an inspiration to expiration ratio of 1:2. This technique can be used frequently throughout the day, in 5-10 minute bursts (or longer if helpful).[20]

Pulmonary Rehabilitation. Many patients are still recovering spontaneously in the first six weeks after acute COVI-19 infection and do not generally require fast-track entry into a pulmonary rehabilitation programme. Those who have had significant respiratory illness may benefit from pulmonary rehabilitation, defined as "a multidisciplinary intervention based on personalised evaluation and treatment which includes, but is not limited to, exercise training, education, and behavioural modification designed to improve the physical and psychological condition of people with respiratory disease." In the context of COVID-19, rehabilitation is being delivered by various virtual models, including video linked classes and home education booklets with additional telephone support.[20]

Pulse Oximetry Self Monitoring. Hypoxia may reflect impaired oxygen diffusion and is a recognized feature of COVID-19. It may be asymptomatic or symptomatic. Oxygen saturation probes (pulse oxymeters) have been used as part of a package of care for patietns with COVID-19. Patients should be provided with pulse oxymeter and an observasional diary and given instructions for how to perform self monitoring. This would be a daily reading taken on a clean, warm finger without nail polish, after resting for 20 minutes; the device should be left to stabilize and the highest reading obtained should be recorded. The target range for oxygen saturation as 94-98% and a level of 92% or below as requiring supplementary oxygen (unless the patients is in chronic respiratory failure. Normal assessment without red flag, an oxygen saturation of 96% or above and the absence of desaturation on exertional test is very reassuring. Oxymeter readings persistenly in the 94-95% range or below require assessment and further investigation. Appropriate adjusments should be made for patients with lung disease and known-in whom the range of 88-92% is considered acceptable.[20]

CONCLUSION

Severe acute respiratory tract infection due to COVID-19 infection is an extremely serious disease. One of the complications of respiratory system infection is pulmonary fibrosis, leading to permanent disability. Diagnosis of pulmonary fibrosis can be made based on history of suffering from severe ARDS, following by clinical symptoms and characteristic pattern of pulmonary fibrosis from CT scan finding. There are few options available for its treatment. The most important factor in limiting pulmonary fibrosis is timely antiviral treatment and elimination of the causative agent. There is no fully definitive treatment for post-inflammatory pulmonary fibrosis after COVID-19 infection. Antifibrotic therapies may be considered consisting of pirfenidone, nintedanib and MSCs. Beside medical treatment, pulmonary rehabilitation program and longterm oxygen treatment should be included as part of comprehensive treatment for pulmonary fibrosis due to COVID-19.

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