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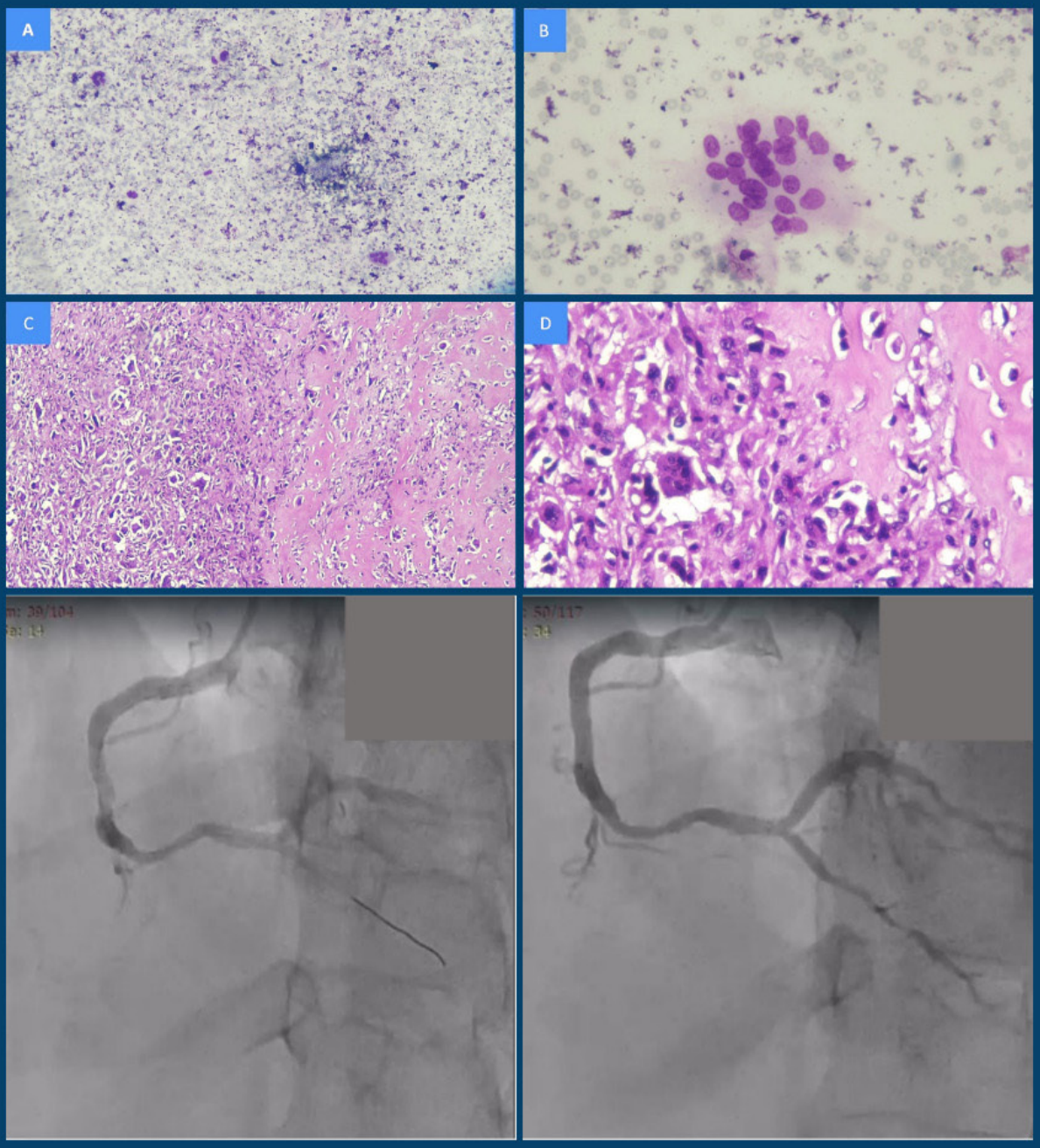

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The correlation between interleukin-4 (IL-4) and programmed cell death-ligand 2 (PD-L2) expression with clinicopathological characteristics on prostate cancer

Ragil Unggul Prakoso[1], Raden Danarto[1]*, Indrawarman Soerohardjo[1], Yurisal Akhmad Dany[1], Ery Kus Dwianingsih[2]

[1]Division of Urology, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/dr. Sardjito Hospital, Yogyakarta, Indonesia, [2]Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/dr. Sardjito Hospital, Yogyakarta, Indonesia

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ABSTRACT

Prostate cancer (PCa) is the most frequent cancer diagnosed worldwide and the second most common malignancy in men. IL-4 is one of cytokines related to the inflammation process. An increase level of IL-4 in patients with PCa might be related to progression to castrate-resistance prostate cancer. Programmed cell death-ligand 2 (PD-L2) plays an important role in the anti-tumor immune system, however the exact mechanism is not fully understood. This study aimed to investigate the correlation between IL-4 and PD-L2 expression with the clinicopathological characteristic of PCa. The IL-4 and PD-L2 examinations were performed using quantitative real-time polymerase chain reaction (qRT-PCR) while clinicopathological characteristics were described by the Gleason score and International Society of Urological Pathology (ISUP) grade. Data collected were then analyzed using Pearson and Spearman test. In total, 20 patients with PCa tissue were collected between 2015 and 2020. The mean level of IL-4 and PD-L2 were higher in metastatic PCa/M-PCa (105.64 and 665.42 ng/mL) compared to non-metastatic PCa/NM-PCa (41.62 and 215.06 ng/mL). A significant difference with medium correlation between IL-4 and PD-L2 with Gleason score and ISUP grade was observed on all samples (p = 0.035 and 0.045; r = 0.454 and 0.473). However, no significant difference with weak correlation was observed on each group (p = 0.136 and 0.858; r = 0.065 and 0.506). Interestingly, there was a significant difference with very strong correlation observed between IL-4 and PD-L2, both on all samples (p = 0.001; r = 0.955) and on each group (p = 0.001 and 0.001; r = 0.917 and 0.955). In conclusion, there is a correlation between IL-4 and PD-L2 with the clinicopathological characteristics of PCa.

Keywords:
clinicopathological;
IL-4;
mRNA;
PD-L2;
prostate cancer

ABSTRAK

Kanker prostat (PCa) adalah kanker yang paling sering terdiagnosis di seluruh dunia dan merupakan keganasan kedua paling umum pada pria. IL-4 merupakan salah satu sitokin yang berhubungan dengan proses inflamasi. Peningkatan kadar IL-4 pada pasien PCa berhubungan dengan perkembangan kanker prostat kebal kastrasi. *Programmed cell death-ligand* 2 (PD-L2) mempunyai peran penting dalam sistem kekebalan anti tumor, namun mekanisme pastinya belum sepenuhnya dipahami. Penelitian ini bertujuan untuk mengkaji hubungan ekspresi IL-4 dan PD-L2 dengan karakteristik patologi klinik PCa. Pemeriksaan IL-4 dan PD-L2 dilakukan dengan *quantitative real-time polymerase chain reaction* (qRT-PCR) dan karakteristik patologi klinik digambarkan dengan *Gleason score* dan *International Society of Urological Pathology* (ISUP) *Grade*. Data yang terkumpul kemudian dianalisis menggunakan uji Pearson dan Spearman. Total 20 pasien dengan jaringan PCa dikumpulkan antara tahun 2015 dan 2020 dan dianalisis. Rerata kadar IL-4 dan PD-L2 lebih tinggi pada PCa metastasis /M-Pca (105,64 dan 665,42 ng/mL) dibandingkan dengan PCa non-metastasis/NM-PCa (41,62 dan 215,06 ng/mL). Terdapat perbedaan signifikan dengan korelasi sedang antara IL-4 dan PD-L2 dengan *Gleason score* dan ISUP *grade* pada semua sampel (p = 0,035 dan 0,045; r = 0,454 dan 0,473). Namun, tidak ada perbedaan nyata dengan korelasi lemah pada masing-masing kelompok (p = 0,136 dan 0,858; r = 0,065 dan 0,506). Menariknya, terdapat perbedaan nyata dengan korelasi sangat kuat antara IL-4 dan PD-L2 yang diamati pada semua sampel (p = 0,001; r = 0,955) dan setiap kelompok (p = 0,001 dan 0,001; r = 0,917 dan 0,955). Kesimpulannya, terdapat hubungan antara IL-4 dan PD-L2 dengan karakteristik patologi klnik PCa.

*corresponding author: dr.danarto@yahoo.co.id

INTRODUCTION

Nowadays, prostate cancer (PCa) is the most frequent cancer diagnosed worldwide. It is the fourth most non-skin cancer in human and the second most diagnosed cancer in men in the world. In 2018, approximately 1.3 million new cases of PCa were diagnosed and 359.000 deaths occurred. Prostate cancer is positioned as the fifth cause of death in men worldwide.[1] Early diagnosis and management of PCa contribute to the decrease of mortality rate in many countries such as in the United States, North America, Oceania, North and West Europe, and several developing countries in Asia.[1-4]

Chronic inflammation has emerged as an important factor in the development and progression of PCa through the release of proinflammatory cytokines. It was reported that interleukin-4 (IL-4), an inflammatory mediator, plays a dual role in the development and progression of PCa.[5,6] On one hand, IL-4 was shown to have tumor-promoting effects in prostate cancer. Interleukin-4 induces T-cell anergy and loss of T-cell-mediated cytotoxicity leading to the promotion of tumor development and cancer progression.[7] Moreover, IL-4 serves a direct role in the progression of PCa from androgen-responsive to advanced castrate-resistance PCa. The IL-4 also can activate the androgen receptor (AR) which plays in the transition from androgen-dependent to androgen-independent PCa after androgen therapy.[8] On the other hand, IL-4 also has tumor-suppressive properties in prostate cancer, especially in benign PCa.[5] At high concentrations, IL-4 inhibits the proliferation of breast and colorectal cancer cells line.[9,10] In addition, IL-4 induces natural killer (NK) cell cytotoxicity and increases NKG2D receptor expression.[11]

Programmed cell death-ligand 2 (PD-L2) is one of two ligands of the programmed cell death-1 (PD-1) receptor, a protein that plays an important role in immune cell activation. It has been widely used as targeted therapy in some solid tumor and hematology cancers with promising results.[12] Programmed cell death-ligand 2 plays a role in the regulation of antitumor immune response, however, the exact mechanism can not be fully explained.[13] The high expression of PD-L2 in prostatectomy samples also shows a prognostic value with the findings of worse biochemical recurrence, metastatic status, and specific survival in prostate cancer.[14] This study aimed to investigate the correlation between IL-4 and PD-L2 with clinicopathological characteristics on PCa patients.

MATERIAL AND METHODS

Study design and subject

This was an observational cross-sectional study involving twenty paraffin embedded tissue samples of PCa patients in the Dr. Sardjito General Hospital, Yogyakarta, Indonesia, from 2015 to 2020 who meet the inclusion and exclusion criteria. The PCa patients were diagnosed based on the histopathological examination either from prostate biopsy or transurethral resection of the prostate. The inclusion criteria of samples were PCa patients with available paraffin embedded tissue samples and complete pathological anatomy grading. The exclusion criterias were tissue samples aged more than 3 years and had invalid DNA integrity.

This study has been approved by the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta with number KE/FK/0109/EC/2022.

Examination of IL-4 and PD-L2 expression

RNA extraction

The RNA genome was extracted from formalin-fixed paraffin-embedded (FFPE) prostate tissue using the GeneAll®

Exgene™ Hybrid™ miRNA Kit (Cat. No. 104-150). In FFPE tissue specimens, a deparaffinization procedure was carried out using xylol and absolute ethanol. Cell lysis was carried out using FARB buffer and 3.5 μL β-mercaptoethanol. For RNA binding and elution, ethanol 70% (RNase-free) was used, and then RNA was extracted.

RT-qPCR

The RNA extraction product was then examined using the Bioneer AccuPower® GreenStar™ RT-qPCR PreMix (Cat. No. K-6400). The PCR was performed using veriti thermal cycler under the following conditions: reverse transcription at 50-70°C for 15 min followed by 1 cycles of pre-denaturation at 95°C for 5 min, denaturation at 95°C for 30 sec, 40 cycles annealing/extension/detection at 55-60°C for 30 sec, and 1 cycle of melting. The primer used was Bioneer Oligonucleotide - AccuOligo® which has free bio-RP purification (Cat. No. SR-1002)

Prostate cancer classification

The PCa classification was created to group patients with similar clinical findings. Generally, it was used to determine the stage of the disease and to decide the most appropriate management.[15]

TABLE 1. TNM classification of PCa

Class	Characteristics
T- Tumor (primary)	
• Tx	Primary tumor can't be assessed
• T0	No evidence of tumor
• T1	Tumor can't be palpated clinically
• T1a	• Incidental tumor finding ≤ 5 % of the resected tissue
• T1b	• Incidental tumor finding > 5 % of the resected tissue
• T1c	• Tumor identified using needle biopsy
• T2	Tumor can be palpated and confined in prostate
• T2a	• Tumor palpated in less than half of the lobe, in one lobe
• T2b	• Tumor palpated in more than half of the lobe, in one lobe
• T2c	• Tumor palpated in both lobes
• T3	Tumor infiltrate the prostate capsule
• T3a	• Extracapsular extension (unilateral or bilateral)
• T3b	• Tumor infiltrate seminal vesicle
• T4	Tumor is fixated or infiltrate other organ beside seminal vesicle: external sphincter muscle, rectum, levator muscle and or abdominal wall
N-Node	
• Nx	Regional lymphnode can't be assessed
• N0	Regional lymphnode metastatic is absent
• N1	Regional lymphnode metastatic is present
M-Metastatic	
• M0	Distant metastatic is absent
• M1a	Metastatic in non-regional lymphnode
• M1b	Metastatic in bone
• M1c	Metastatic in visceral organ

Note: TNM classification of PCa. T is assessed using digital rectal examination (DRE). N and M is assessed using radiologic imaging, the most common used is multi-slice computed tomography (MSCT) with contrast.

In addition, grading in PCa was also needed for the treatment decision. It was also needed to group the disease into risk groups. The Gleason score was measured by finding the most common histopathological pattern type and second most common pattern type, while ISUP grade was grouped according to its Gleason score.[15]

Statistical analysis

The SPSS version 25.0 was used for statistical analysis. The data were previously tested for the normality using Saphiro Wilk test. The correlation between variables were analyzed using Pearson analysis for normally distributed data and using Spearman analysis for data that not normally distributed. A p value < 0.05 was considered significant.

RESULTS

Twenty PCa patients were involved in this study. The patients were divided into two groups with 10 patients in each group i.e. metastasis prostate cancer (M-PCa) and non-metastasis prostate cancer (NM-PCa). The mean age for M-PCa group was 69.6 ± 9.51 yr, while in NM-PCa group was 75.7 ± 5.52 yr. The IL-4 and PD-L2 expression as well as Gleason score and ISUP grade on PCa patients are presented in TABLE 3.

Significant moderate positive correlation ($r > 0.400$; $p < 0.05$) between IL-4 and PD-L2 with clinicopathological characteristics (Gleason score and ISUP grade) on group of PCa was observed (TABLE 4). However, no significant correlation ($p > 0.05$) on subgroup of PCa was observed (TABLE 5).

Interestingly, strong correlation between IL-4 and PD-L2 both in group or subgroup of PCa was observed ($r>0.900$; $p < 0.05$) as presented in TABLE 6 and FIGURE 1A and 1B.

TABLE 2. Prostate cancer grading according to the International Society of Urological Pathology

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8	4
9-10	5

Note: Gleason score and ISUP grade as the part of prostate cancer grading to know disease severity and guide for management decision.

TABLE 3. IL-4 and PD-L2 expression (ng/mL) and Gleason score and ISUP grade on PCa patients

Variable	n	Mean ± SD	Med. (Min. – Max.)
IL-4			
• NM-PCa	10	41.628 ± 19.85	41.62 (17.15 – 68.59)
• M-PCa	10	105.64 ± 26.81	105.64 (73.52 – 168.9)
PD-L2			
• NM-PCa	10	215.061 ± 117.41	215.06 (64.0 – 415.87)
• M-PCa	10	665.424 ± 204.16	665.42 (445.72 – 1024.0)
Gleason score			
• NM-PCa	10	7.6 ± 1.58	7.6 (6 – 10)
• M-PCa	10	9 ± 1.25	9 (6 – 10)
ISUP grade			
• NM-PCa	10	2.9 ± 1.73	2.9 (1 – 5)
• M-PCa	10	4.5 ± 1.27	4.5 (1 – 5)

Note: SD= standard deviation; Med. = median; Min. = lowest value; Max. = highest value; PCa: prostate cancer; NM-PCa = non-metastasis prostate cancer; M-PCa = metastasis prostate cancer (NM-PCa); PD-L2 = programmed cell death-ligand 2; ISUP grade = The International Society of Urological Pathology grade.

TABLE 4. Correlation between IL-4 and PD-L2 with Gleason score and ISUP on group of PCa

Variable	r	p
IL-4 – Gleason score	0.470	0.036
IL-4 – ISUP grade	0.454	0.045
PD-L2 – Gleason score	0.473	0.035
PD-L2 – ISUP grade	0.454	0.044

Note: PCa: prostate cancer; PD-L2 = programmed cell death-ligand 2; ISUP grade = The International Society of Urological Pathology grade.

TABLE 5. Correlation between IL-4 and PD-L2 expression with Gleason score and ISUP grade on subgroup of PCa

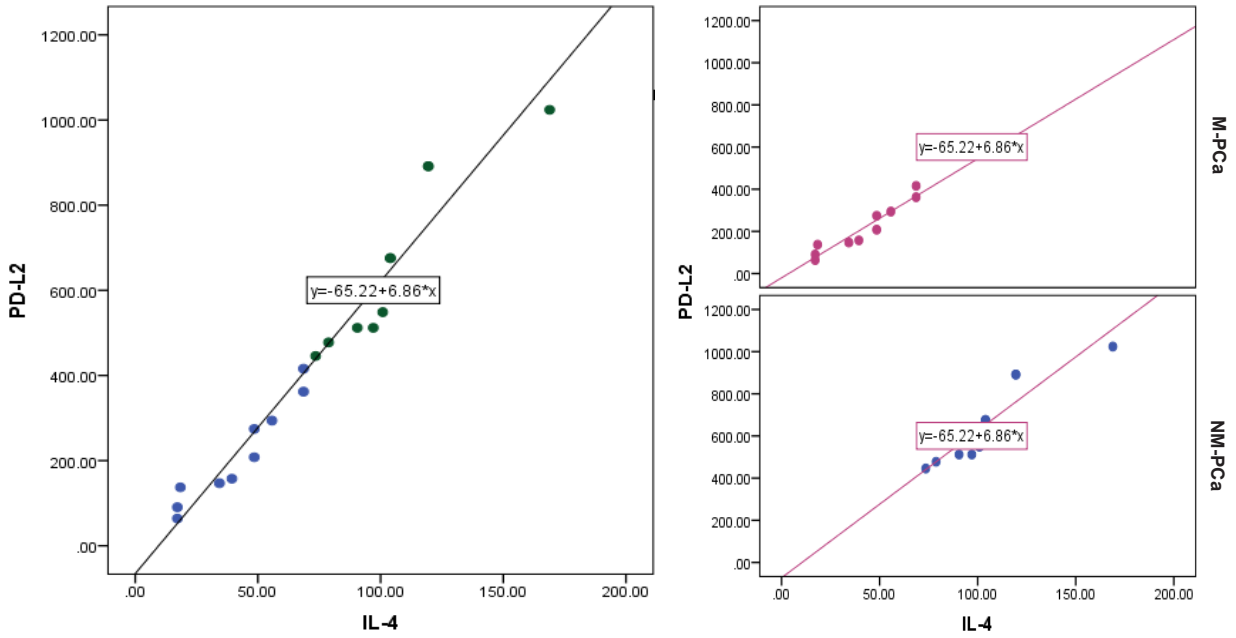
Variable	r	p
IL-4 – Gleason score		
• NM-PCa	0.145	0.690
• M-PCa	0.504	0.137
IL-4 – ISUP grade		
• NM-PCa	0.176	0.626
• M-PCa	0.065	0.858
PD-L2 – Gleason score		
• NM-PCa	0.162	0.655
• M-PCa	0.506	0.136
PD-L2 – ISUP grade		
• NM-PCa	0.181	0.617
• M-PCa	0.065	0.857

Note: PCa: prostate cancer; NM-PCa = non-metastasis prostate cancer; M-PCa = metastasis prostate cancer (NM-PCa); PD-L2 = programmed cell death-ligand 2; ISUP grade = The International Society of Urological Pathology grade.

TABLE 6. Correlation analysis between IL-4 and PD-L2 expression in all group and subgroup

Variable	r	p
All samples	0.950	0.001
NM-PCa	0.955	0.001
M-PCa	0.917	0.001

Note: NM-PCa = non-metastasis prostate cancer; M-PCa = metastasis prostate cancer (NM-PCa); PD-L2 = programmed cell death-ligand 2.



A B

FIGURE 1. Scatterplot for correlation of IL-4 and PD-L2 on A) group and B) subgroup of PCa.

DISCUSSION

Correlation between IL-4 and PD-L2 with Gleason score and ISUP grade on all group

Significant moderate positive correlation between IL-4 and PD-L2 with clinicopathological characteristics on group of PCa were observed (TABLE 4). In this study the clinicopathological of PCa was expressed by Gleason score and ISUP grade. The increase of Gleason score was followed by the increase of ISUP grade as the Gleason score is the component in ISUP grade measurement. The increase of both of this clinicopathological aspect is related to advance prostate cancer. This is similar to the results reported by Erb *et al.*[16] stating that IL-4 as one of cytokines which affects the immune response, cell proliferation, differentiation, and related to prostate cancer and tumor microenvironment (TME). IL-4 was found a lot in cell in TME, such as tumor-associated stromal cells and tumor-infiltrating immune cells,

and this is known to be increasing significantly in patients with advance prostate cancer.

Significant moderate positive correlation between PD-L2 with clinicopathological characteristics on group of PCa observed in this study was also reported by Zhao *et al.*[17] The authors demonstrated that PD-L2 affects the immune system response in the development of prostate cancer. Not like PD-L1, studies concerning PD-L2, one of ligands of PD-1, were limited. Even though PD-L2 has two until six time higher affinity compared to that PD-L1.[12] The role of PD-L1 and PD-L2 in the progressivity of prostate has not been clearly explained. Both PD-L1 and PD-L2 may bond to PD-1 receptor in T cell lead to increase prostate cancer cell proliferation.

Correlation of IL-4 and PD-L2 with Gleason score and ISUP grade on each group

Although significant moderate positive correlation between IL-4 and PD-L2 with clinicopathological characteristics (Gleason score and ISUP grade) on all group of PCa were observed, however there was no significant correlation ($p > 0.05$) on subgroup of PCa (TABLE 5). This result is not concordance with other previous studies. Relatively little sample involving in each group (10 samples) in this study might cause the correlation was not significant. Very low correlation in NM-PCa group and low correlation in M-PCa were observed. This result was also supported by the higher of the mean of IL-4 and PD-L2 in M-PCa. Goldstein *et al.*[5] reported that IL-4 proportionally increase with the PCa development, both in castrate-resistance and M-PCa. IL-4 activates androgen receptor in PCa cell, even in the condition of low circulating level of androgen. Moreover, Zhang *et al.*[14] reported that the increase of PD-L2 level is associated with worst biochemical recurrence, metastatic status, and cancer specific survival in PCa.

Correlation of IL-4 with PD-L2

Solinas *et al.*[12] reported that PD-L2 expression was identified in a variety of tumor cells including tumor-associated macrophages (TAMs), and tumor-infiltrating lymphocytes (TILs), dendritic cells tumor, and stromal cells tumor, which able to induce the release some cytokines such as IL-4, granulocyte-monocyte colony stimulating factor (GM-CSF), IF-γ and IF-β. The PDL-2 expression in esophagus cancer cells is associated to Th2 response mediated by IL-4 and IL-13. Whereas in colorectal cancer cells, it is mediated by IFN-γ and in melanoma, it is mediated by IFN-β and IFN-γ.

A significant strong correlation between IL-4 and PDL-2 both in M-PCa and NM-PCa was observed in this study (TABLE 6 and FIGURE 1). However, the reason underlying the correlation between IL-4 and PDL-2 in PCa can not be explained in this study. Further study is needed to explain the correlation.

This study used limited samples, 10 samples for M-PCa and 10 samples for NM-PCa, which might not represent the general population. Previous studies concerning this topic are also limited. Further studies are needed to prove the findings of this study.

CONCLUSION

In conclusion, there is correlation between IL-4 and PD-L2 with the clinicopathological characteristics of patients with PCa. In addition, a strong correlation between IL-4 and PD-L2 is reported in patients

with PCa. Further study with larger samples is needed to be conducted to confirm this finding.

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No conflict of interest is declared in this study.

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Characteristics of patients associated with antibiotic use among gastrointestinal surgery at the Academic Hospital, Universitas Gadjah Mada

Pingki Arum Saskiya, Taufiqurohman, Chairun Wiedyaningsih*
Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta
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ABSTRACT

Digestive surgery is a treatment for diseases of the parts of the body involved in digestion, which has a fairly high risk of infection. The study aimed to obtain a description of the types and specific characteristics of patients and the rationality of antibiotic use among digestive surgery patients. This study was conducted using observational analysis. Data on antibiotic use was collected prospectively from medical records of digestive surgery inpatients at the Academic Hospital Universitas Gadjah Mada (UGM) from January to March 2023. The Gyssens method was used to evaluate qualitatively the use of antibiotics. A total of 76 patients met the inclusion and exclusion criteria. No significant difference between the number of male and female patients was identified. The results showed that 24 (31.58%) acute appendicitis patients are the primary diagnosis most often encountered in patients undergoing digestive surgery. The most frequently used prophylactic antibiotics for digestive surgery patients were ceftriaxone (53.85%) and cefazolin (41.03%). Meanwhile, the most frequently used therapeutic antibiotics were ceftriaxone (41.94%) and levofloxacin (29.03%). The Gyssens analysis shows that large irrational use of antibiotics is still observed.

ABSTRAK

Bedah digestif merupakan pengobatan penyakit pada bagian tubuh yang berhubungan dengan pencernaan yang memiliki risiko infeksi cukup tinggi. Penelitian ini bertujuan untuk memperoleh gambaran tentang jenis dan karakteristik spesifik pasien serta rasionalitas penggunaan antibiotik pada pasien bedah digestif. Penelitian ini dilakukan dengan menggunakan analisis observasional. Data penggunaan antibiotik dikumpulkan secara prospektif dari rekam medis pasien rawat inap bedah digestif di Rumah Sakit Akademik Universitas Gadjah Mada (UGM) pada Januari hingga Maret 2023. Metode Gyssens digunakan untuk mengevaluasi penggunaan antibiotik secara kualitatif. Sebanyak 76 pasien memenuhi kriteria inklusi dan eksklusi. Tidak ada perbedaan yang signifikan antara jumlah pasien laki-laki dan perempuan. Hasil penelitian menunjukkan bahwa 24 (31,58%) pasien apendisitis akut merupakan diagnosis utama yang paling sering ditemui pada pasien yang menjalani bedah digestif. Antibiotik profilaksis yang paling banyak digunakan pada pasien bedah digestif adalah seftriakson (53,85%) dan sefazolin (41,03%). Sedangkan antibiotik terapeutik yang paling banyak digunakan adalah seftriakson (41,94%) dan levofloksasin (29,03%). Analisis dengan metode Gyssens menunjukkan masih banyak dijumpai penggunan antibiotik yang tidak rasional.

Keywords:
digestive surgery;
antibiotic;
gyssens;
drug use;
rationality

INTRODUCTION

Millions of surgical are performed in the world annually. Sometimes, complications can occur following surgery.[1] combined general surgery

*corresponding author: chairun_wied@ugm.ac.id

and trauma, vascular surgery, and cardiothoracic surgery. Main Outcome Measures: Total complication rate (number of complications divided by the number of patients.[2] Surgical site infection is one of the most common complications of abdominal surgery.[3] Surgical site infections are caused by bacteria that enter through incisions made during surgery.[4] Approximately 0.5 to 3% of patients undergoing surgery will experience infection, associated with length of stay (LoS).[5] Gillespie *et al.*[6] reported that 11 out of 100 general surgery patients will likely experience an infection 30 d after surgery.

Surgical care is an essential component of health care. They are threaten the lives of millions of patients each year and contribute to the spread of antibiotic resistance.[4] Surgical site infection estimates varied among the World Health Organization (WHO) regions.[7] Surgical site infections are preventable, and various interventions have been proposed over the past years.[8] Syaiful *et al.*[9] reported that of 4,893 abdominal operations during the study period, 135 subjects (2.8%) experienced surgical site infection, with 42.2% of cases being the clean contamination type. Even though the surgical site infection at Dr. Cipto Mangunkusumo General Hospital is low, attention is still needed to address this problem.[9] The incidence of surgical wound infections can be reduced by administering prophylactic antibiotics before surgery.

The antibiotic prophylaxis is a very brief course of antibiotics initiated closely before,[10] during and after the operative procedures to prevent infectious complications or surgical site infections,[11,12] while it was considered therapeutic when it was prescribed to treat existing disease.[12] However, using prophylactic antibiotics in clinical practice must follow the existing guide. The government has issued the regulation of the Minister of Health of Republic of Indonesia number 28/2021 concerning General Guidelines for the Purposeful Use of Antibiotics as a reference in optimizing the wise use of antibiotics. Inappropriate use of surgical prophylactic antibiotics has been widely reported.[10,12-15] If the antibiotics used in surgical patients are inappropriate, there will be a risk of resistance. Therefore, monitoring the use of prophylactic and empiric antibiotics in surgical patients is necessary.

MATERIAL AND METHODS

Study design

An observational analysis method was used in this study. The use of prophylactic antibiotics and patient clinical outcomes were collected prospectively from medical records in the inpatient ward of the Academic Hospital, Universitas Gadjah Mada (UGM), from January to March 2023. The medical record data was also used to collect demographic patients and management of digestive surgery patients. This study's inclusion and exclusion criteria were inpatients undergoing digestive surgery who received antibiotics before surgery and/or during hospitalizations and age ≥ 5 yr. Exclusion criteria included incomplete data such as not recording the operation time, antibiotic use, and timing of antibiotic administration; paralyzed/coma patients, diabetics, immunocompromised patients, and patients undergoing treatment chemotherapy. The sample used in this research was determined using the Slovin formula.[16] It was known that the population of digestive surgery patients at the Academic Hospital, UGM during the last three months was 305. The level of precision set was 10%. The minimum number of samples that meet the criteria was 76.

Data analysis

The types and specific characteristics of patients and the antibiotic use was analyzed descriptively. Analysis of the rationality of antibiotic use was carried out using the flow diagram Gyssens method.[17] The main antibiotic guideline based on the Regulation of the Minister of Health of the Republic of Indonesia number 28/2021 about Guidelines for Use of Antibiotics. The American Society of Health System Pharmacists (ASHP) Therapeutic and some other guidelines were also used to support the evaluation. If the antibiotic administered was not listed in the main guideline, then the search was continued in the Guidelines for Use of Antibiotics. The ASHP or related journals. Antibiotics were called prophylaxis if they were given before, during and after a surgical procedure or a maximum of 24 hr from the first administration. If antibiotics were given from the time the patient first arrives and was treated at the hospital until the patient goes home, then the antibiotic was classified as a therapeutic antibiotic. The quality evaluation of the use of antibiotics was carried out by the researcher together with pharmacist and surgeon. This was intended to reduce subjectivity in the evaluation process. The results are presented descriptively and supported by tables.

Ethics approval

This research has been approved by the Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, UGM with ref. no. KE/FK/1584/EC/2022. This research has also received a permit from the Academic Hospital, UGM with number–1380/UN1/RSA.2/AR/SB/2023.

RESULTS

A total 105 digestive surgery patients' data were taken from medical records. Of the samples taken, 76 patients met the inclusion criteria, and 29 met the exclusion criteria. Patients who did not meet the inclusion criteria were patients aged under five. Meanwhile, 17 patients included in the exclusion criteria due to incomplete data included patients who underwent surgery in the final week of data retrieval. The other eight patients who met other exclusion criteria were patients with comorbid diabetes. TABLE 1 shows an overview of the demographic characteristics of digestive surgery inpatients at the Academic Hospital UGM, January-March 2023. No significant difference between the number of male and female patients was observed. Of the 76 digestive surgery patients, 39 (51.32%) were males, and 37 (48.68%) were females. The study showed that patients aged 19 – 44 yr 34 (44.74%) were the most patients undergoing digestive surgery.

TABLE 2 shows the disease characteristics of inpatients undergoing digestive surgery at the Academic Hospital UGM from January to March 2023, including primary diagnoses and comorbidity. The study shows that 24 (31.58%) patients underwent digestive surgery, with the primary diagnosis being acute appendicitis (K35.9), while the most common comorbidity was hypertension, 8 (22.86%) patients.

TABLE 1. Characteristics of inpatient digestive surgery at the Academic Hospital UGM for the period January-March 2023

Patient characteristics	Number of patients [n (%)]
Gender	
• Male	39
• Female	37
Subtotal	76 (100)
Age	
• >5 – 18 yr	9
• 19 – 44 yr	34
• 45 – 59 yr	15
• >60 yr	18
Subtotal	76 (100)

TABLE 2. Disease characteristics of digestive surgery inpatient at Academic Hospitals UGM period January-March 2023

Disease characteristics	ICD X code	Number of patients [n (%)]
Primary diagnosis		
• Appendicitis acute	K35.9	24 (31.58)
• Cholecystitis	K81.0	11 (14.47)
• Inguinal hernia	K40.90	7 (9.21)
• Ileus obstructive	K56.7	6 (7.89)
• Cholelithiasis	K80	5 (6.58)
• Tumor	C80.1	4 (5.26)
• Chronic appendicitis	K36	3 (3.95)
• Peritonitis ec perforation	K65	3 (3.95)
• Haemorrhoids	K64.9	2 (2.63)
• Prolapse recti	K62.3	2 (2.63)
• Cholelithiasis + cholecystitis	K80.63	1 (1.32)
• Others		8 (10.53)
Subtotal		76 (100)
Comorbidity		
• Hypertension	I10	8 (22.86)
• Hyponatremia	E87	6 (17.14)
• Hypokalaemia	E87.6	4 (11.43)
• Anaemia	D64.9	4 (11.43)
• Diarrhoea	R19.7	3 (8.57)
• AKI	N17	2 (5.71)
• Febris/hyperpyrexia	R50	2 (5.71)
• Gastroenteritis	K52.9	1 (2.86)
• Hydronephrosis	N13.2	1 (2.86)
• Urinary tract infection	N12	1 (2.86)
• Pelvic inflammatory disease	N73.9	1 (2.86)
• Tuberculosis	A15	1 (2.86)
• Thrombocytopenia	D69.6	1 (2.86)

Noted: Not all patients have comorbidities, and one patient can have more than one comorbidity

Data related to the description of the surgical management of digestive inpatients at the Academic Hospital UGM period January – March 2023 is presented in TABLE 3. Surgical reports listed in the medical records of inpatients undergoing digestive surgery included surgical procedures, operation plan, duration of operation, and length of stay before surgery. The most common surgical procedure performed was appendectomy in 29 (38.16%) cases. The study shows that 65 (85.53%) cases of surgical procedures were carried out electively, and the time from incision to the closing of the surgical wound was generally less than 1 hr in 34 (44.74%) patients. There were 62 (81.58%) patients with a more extended stay before surgery of < 3 d. The present study shows that emergency surgery was performed on appendectomy in 9 cases, hernia repair in 1 case, and recti prolapse in 1 patient.

TABLE 3. The management of digestive surgery inpatients at Academic Hospital UGM period January-March 2023

Surgical characteristics	Number of patients [n (%)]
Surgical action	
• Appendectomy	29 (38.16)
• Cholecystectomy	18 (23.68)
• Herniorepair	8 (10.53)
• Operative laparoscopy	8 (10.53)
• Exploratory laparotomy	4 (5.26)
• Low resection	2 (2.63)
• Haemorrhoidectomy	2 (2.63)
• Recti prolapse	2 (2.63)
• Perianal fistulectomy	1 (1.32)
• Gastrostomy, ileostomy, colostomy	1 (1.32)
• Gastric anatomy resection	1 (1.32)
Sub total	76 (100)
Operation Plan	
• Elective	65 (85.53)
• Cito	11 (14.47)
Sub total	76 (100)
Duration of surgery	
• <1 hr	34 (44.74)
• 1 – 2 hr	35 (46.05)
• >2 hr	7 (9.21)
Sub total	76 (100)
LoS before surgery	
• <3 d	62 (81.58)
• ≥3 d	14 (18.42)
Sub total	76 (100)

The use of antibiotics for inpatients with digestive surgery was grouped into prophylactic antibiotics, therapeutic antibiotics, and both of them. The results showed that 14 (17.11%) patients received prophylactic antibiotics, 37 (50%) received therapeutic antibiotics, and 25 (32.89%) patients received both of them. The study shows that all gastrointestinal surgical patients on prophylactic antibiotic therapy received single antibiotic therapy. The type of prophylactic antibiotic most frequently used for digestive surgery patients was ceftriaxone in a total of 21 (53.85%) patients, followed by cefazolin in 16 (41.03%) patients and levofloxacin in 2 (5.13%) patients. The therapeutic antibiotics given are categorized as empirical antibiotics because the bacterial culture was usually not performed on digestive surgery patients; the study shows that patients undergoing digestive surgery were given single or combination therapeutic antibiotics. The single type of therapeutic antibiotic most frequently given to digestive surgery patients was ceftriaxone in 26 (41.94%), followed by levofloxacin in 18 (29.03%) patients. Meanwhile, the type of combination therapeutic antibiotics most frequently given to digestive surgery patients was ceftriaxone + metronidazole for 13 (20.97%) patients, followed by cefotaxime + metronidazole for (8.06%) patients.

The rationality of antibiotics was evaluated using the Gyssens method[17]the pathogens, and the anti-infective agents. The rational use of antimicrobial drugs is based on an understanding of the many aspects of infectious diseases. Factors relating to host defence, the identity, virulence, and susceptibility of the microorganism and the pharmacokinetics and pharmacodynamics of antimicrobial drugs have to be considered. Antimicrobial use is the major determinant of microbial resistance. To guarantee the long-term efficacy of antimicrobial drugs, the quality-of-use should be maximised and overconsumption (inappropriate use and with the main guidelines of the Minister of Health of Republic of Indonesia No. 28/2021 concerning Antibiotic Use and the Antimicrobial Use Guidelines 2023 of the Academic Hospital UGM. The rationality for the use of prophylactic and therapeutic antibiotics is presented in TABLE 4. From January – March 2023, of 76 digestive surgery patients, 39 were given prophylactic antibiotics. Analysis of antibiotics use through the flow diagram of the Gyssens method resulted in the rational category (category 0) of 2 (5.13%) patients and 37 (94.87%) patients who were irrational. The results also show two patients with prophylactic antibiotics in category IVA (other antibiotics are more effective). Thus, both patients received a cholecystectomy with prophylactic antibiotic levofloxacin. The IVD category is a category that indicates the presence of other antibiotics with a narrower spectrum. The results of the analysis showed that 21 patients underwent digestive surgery (13 appendectomies, three exploratory laparotomies, and one each of cholecystectomy, perianal fistulectomy, gastrostomy, ileostomy, colostomy, low resection, and prolapse recti) given ceftriaxone as a prophylactic antibiotic. Therefore, it was an IVD category.

TABLE 4. Rationality of the use of prophylactic and therapeutic antibiotics inpatients of digestive surgery at the Academic Hospital UGM for the period January-March 2023

Rationalities	Category	Number of patients n (%)
Prophylaxis antibiotics (n =39 patients)		
• Rational (n =2 patients)	0	2 (2.63)
• Irrational (n =37 patients)	IVA	2 (2.63)
	IVD	21 (27.63)
	IIA	27 (35.53)
	I	24 (31.58)
Therapeutic antibiotics (n =62 patients)		
• Rational (n =16 patients)	0	17 (25.37)
• Irrational (n =46 patients)	IVA	27 (40.30)
	IB	4 (5.97)
	IIA	6 (8.96)
	IIB	13 (19.40)

Note: Analyzed based on Gyssens. The use of one antibiotic can result in irrationality >1 category. Therfore, the number of analysis results differs from the number of antibiotics.

The present study also showed 27 adult patients (>19 y.o.) with prophylaxis antibiotic category II A (in appropriate doses). The number of surgery, as well as drugs and doses used, as follows: 13 appendectomies with ceftriaxone (1 g); 3 herniorepair with cefazolin (1 g); 1 cholecystectomy with ceftriaxone (1 g); 3 exploratory laparotomy with ceftriaxone (1 g); low resection with ceftriaxone (1 g); low resection with cefazolin (1 g); prolapse recti with ceftriaxone (1 g); prolapse recti with cefazolin (1 g); perianal fistulectomy with ceftriaxone (1 g); gastrostomy, ileostomy, colostomy with ceftriaxone (1 g); and operative laparoscopy with cefazolin (1 g). Inappropriate time use of prophylactic antibiotics (category I) was administration of antibiotics more than 60 min before the procedure. According to guidelines, prophylactic antibiotics are given within 30-60 min before incision. The results showed that were 13 patients given prophylactic antibiotics more than 1 hour before the procedure, and 11 were given prophylactic antibiotics > 2 hr before the incision.

Among 76 digestive surgery patients from January to March 2023, 62 patients received therapeutic antibiotics. Rational use of therapeutic antibiotics (category 0) was 16 (25.81%) patients, and irrational was 46 (74.19%) patients. There were 27 patients with therapeutic antibiotics in the category IVA, including (17 acute appendectomies, three inguinal hernias, three obstructive ileuses, two cholecystitis, and one haemorrhoid), each used ceftriaxone, and only 1 for acute appendicitis treatment used levofloxacin as a therapeutic antibiotic. Four patients were in category IIIB (too short in antibiotic use). In the primary diagnosis of acute appendicitis, 2 patients used it for 3 d, and one patient used it for 2 d. Meanwhile, in the main diagnosis of cholelithiasis,

one patient used it for 5 d. Six patients received therapeutic antibiotics in the category of inappropriate use (category IIA), including three patients with the combination antibiotic cefotaxime + metronidazole, two patients with the combination antibiotic ceftriaxone + metronidazole, and one patient with the antibiotic levofloxacin. Thirteen patients received antibiotics at inappropriate intervals (category IIB), consisting of 12 patients diagnosed with cholecystitis and cholelithiasis given therapeutic antibiotics with levofloxacin at a dose of 500 mg at 24 hr intervals and one patient diagnosed with acute appendicitis given ceftriaxone and metronidazole. Simultaneously at 8 hr intervals. Irrational use of antibiotics was more often found in the use of therapeutic antibiotics. The percentage of irrationality for the use of therapeutic antibiotics reached 40.30% with the most common category being the IVA category (there are other antibiotics that are more effective).

DISCUSSION

The present study shows that the most common primary diagnosis in digestive surgery patients is acute appendicitis (31.58%). Acute appendicitis is one of the most common abdominal emergencies worldwide.[18] Appendicitis is the inflammation of the vermiform appendix.[19] It typically presents acutely, within 24 hr of onset, but can also give as a more chronic condition. Even though there was no significant difference, the results show a tendency for the number of males to be greater than females and the 19 – 44 y.o. group to undergo digestive surgery more often. The results also show that acute appendicitis surgery was the most common cause of digestive surgery patients. Although there is no age exception, appendicitis most often occurs between the ages of 10 and 20 yr.[20] In the United States, there were more males than females, with a ratio of 1.4:1. The overall lifetime risk was 8.6% for males and 6.7% for females.[20] Bhangu *et al.*[18] also stated that most studies show a slight male predominance of acute appendicitis. Appendicitis can occur at any age, but it most commonly affects people in their second or third decade of life, and the disease is less common at both extremes of age.[18] The present study shows that most digestive operations were performed electively, whereas emergency procedures were generally performed in acute appendicitis. Appendectomy is usually carried out on an emergency basis to treat appendicitis (inflamed appendix). If appendicitis occurs, the appendix typically needs to be removed immediately. If left untreated, the appendix can burst, and this is a medical emergency.[21]

Patients who underwent digestive surgery at the Academic Hospital UGM during the research period received only prophylactic antibiotics, some other only therapeutic antibiotics, or they were given both. Surgical antibiotic prophylaxis is associated with reduced surgical site infection rates, hospital stay, and mortality.[11] Surgical antibiotic prophylaxis is a cornerstone of perioperative care.[11] The study shows that ceftriaxone from the cephalosporin group was the single prophylactic antibiotic most often used in digestive surgery. The antibiotic spectrum should be selected according to the local flora of the surgical site.[11] The most widely used antibiotics are first- and second-generation cephalosporin.[11] Based on a systematic review, it was also stated that those included in the top 15 antibiotics most commonly consumed in Indonesia are β-lactams, especially cephalosporin and penicillins.[22] Bacterial culture was not usually performed on digestive surgery patients. The therapeutic antibiotic used in the present study was empirical antibiotics. Similar to the results obtained with prophylactic

antibiotic use, ceftriaxone was the most commonly prescribed therapeutic antibiotic. Meanwhile, the combination therapeutic antibiotic most often given to digestive surgery patients was ceftriaxone + metronidazole. Due to increasing antimicrobial resistance, the correct use of antimicrobials is becoming more complex. The choice of the therapeutic antibiotic should follow current guidelines, take local susceptibility data into account, and reflect the patient's risk factors.[23]

The Gyssens method is an instrument that is widely used to evaluate the appropriateness of using antibiotics in the treatment of patients.[22,24,25] The present study showed various causes of irrational use of antibiotics, either as prophylactic or therapeutic. Both the use of other antibiotics should be more efficient, and the inappropriate doses were the main category that often led to irrational assessments of the use of these antibiotics. The benefits and detriments of each drug should be compared in choosing an antibiotic. Inappropriate use of antibiotics is a reasonably widespread practice worldwide in high-income and low-income nations.[26,27] Improper use of antibiotics can potentially lead to antimicrobial resistance and increase the necessity to use more expensive antibiotics to treat joint and life-threatening infections. Several studies reported on the use of antibiotics for digestive surgery. Surgery involving the gastrointestinal tract provides a special challenge because of its high, predominantly anaerobic bacterial load.[28] The most suitable antibiotic and the optimal duration of prophylaxis are still debated.[29] Better ways of post-operative management of infections must be studied such that the recommended use of antibiotics has complete or specific coverage of pathogens and has minimal adverse effects.[30] Freitas *et al.*,[11] in their study on the use of antibiotics in abdominal surgery, stated that the antibiotic spectrum must be chosen according to the local flora at the surgical site. In addition, antibacterial prophylaxis should cover all possible pathogens, including aerobic and anaerobic organisms.[28] The accepted practice worldwide for preventing surgical site infections is administering single or multiple doses of antimicrobial prophylaxis.[29] Although combination antibiotic therapy is appropriate in certain situations, single-agent prophylaxis is appropriate for most patients.[28] Cefazolin is the most widely used antibiotic for surgical prophylaxis.[11]

Antibiotics are some of the most widely, and often injudiciously, used therapeutic drugs worldwide. Perioperative prophylaxis antibiotic is recommended for various surgical procedures to prevent surgical site infections. The use of therapeutic antibiotics requires consideration including obtaining an accurate diagnosis of infection; identify opportunities to shift to narrow, cost-effective spectrum. In this study, the classification of antibiotic as prophylactic or therapeutic antibiotics was based on the type of surgery, the organ being operated on and the risk of infection/contamination. If surgery was performed on a hollow organ and there was a risk of contamination, prophylactic antibiotics were given. If there was no risk of contamination, then only therapeutic antibiotic was used. The most prevalent form of irrational antibiotic use of the present study was often found in the use of therapeutic antibiotic in the IVA category (there are other antibiotics that are more effective), and in patients with acute appendicitis.

The study found that 40.30% of antibiotics were used irrationally, but no SSI diagnosis. The absence of an SSI diagnosis may be caused by the patient did not having post-operative control as recommended by the doctor. The majority of patients did not comply with post-operative follow-up actions until >30 d after discharge, therefore it was difficult to monitor post-operative

progress. Apart from that, the impact of irrational use does not always result in infection, and vice versa. However irrational use of antibiotics is proving to be a major concern to the health systems globally. This results in antibiotics resistance and increases health care costs.

The irrational use of antibiotic therapy will increase the occurrence of resistance, which impacts the increase of morbidity, mortality, and health costs Worldwide, irrational use of antibiotics is escalating, both in developed and developing countries.[10,13,24,25] Irrational use of antibiotics can take many forms, including the prolonged antibiotics use,[13] restricted antibiotics use,[12] outside clinical guidelines,[13,14] inappropriate timing/ duration of prophylactic or therapeutic antibiotic administration,[10,24,25] or with inadequate dosage or inappropriate route of administration.[12] As a direct consequence of irrational antibiotic use, resistance to the commonly available antibiotics has been increasing rapidly. It is almost impossible to reverse resistance to antibiotics once it is present in the pool of bacteria. Therefore, it is important to always evaluate the use of antibiotics in health services. The spread and emergence of resistance can be slowed before it causes further damage to people's health and finances. This finding remains a challenge to encourage healthcare professionals to appropriately follow hospital guidelines and continually evaluate antibiotic use. The role of the clinical pharmacist can facilitate this process across all surgical disciplines.

Research limitations

Most patients only visited for control after digestive surgery 7 – 14 d and did not by the recommendation for control up to 30 d after digestive surgery. Therefore, the results of the post-operative condition could not be known, and the incidence of wound infection after surgery in patients could not be observed. Apart from that, researchers also did not always know the actual events when determining antibiotic use, including incomplete data on the patient's medical record.

CONCLUSION

In conclusion, patients with acute appendicitis (24 patients or 31.58%) are the highest number among patients undergoing digestive surgery, where most surgical procedures are performed electively, with the time from incision to surgical wound closure generally < 1 hr. The antibiotics most frequently administered to gastrointestinal surgical patients hospitalized during the 3 mo of the study are the cephalosporin group, of which the most widely used is ceftriaxone for prophylaxis (53.85%) and therapeutic (41.94%). The Gyssens analysis shows that the irrational use of antibiotics is still observed. Efforts to increase the rational use of antibiotics among healthcare providers are needed.

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The effectiveness of topical vitamin D_3 for dry skin in elderly

He Yeon Asva Nafaisa[1], Fajar Waskito[1], Rony Martien[2], Retno Danarti[1]*

[1]Dermatology and Venereology Department, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta/ Dr. Sardjito Central General Hospital, Yogyakarta, Indonesia, [2]Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia

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ABSTRACT

Dry skin is one of the most common dermatoses found in the elderly. Vitamin D is an essential fat-soluble vitamin that has a role in repairing the skin barrier. Topical administration of vitamin D_3 is expected to increase skin hydration in the elderly. Thirty-two participants were divided into two groups, namely 5000 IU vitamin D_3 and the base lotion groups. The assessment was carried out by calculating the *overall dry skin score* (ODS), transepidermal water loss (TEWL), and skin capacitance every four week for twelve week. All groups showed an improvement in ODS, a decrease in TEWL, and an increase in skin capacitance value at the end of the measurement, and no significant side effects were reported. The 5000 IU vitamin D_3 lotion group had the highest level of skin hydration compared to the other group ($p>0.05$). We conclude that the administration of 5000 IU vitamin D_3 lotion may be administrated safely and improve skin hydration in the elderly but is not more effective than base lotion.

ABSTRAK

Kulit kering merupakan salah satu permasalahan kulit yang paling banyak dijumpai pada lanjut usia. Vitamin D merupakan vitamin esensial larut lemak yang memiliki peran dalam memperbaiki sawar kulit. Pemberian topikal vitamin D_3 diharapkan dapat meningkatkan hidrasi kulit pada kulit lanjut usia. Jumlah subjek sebesar 32 lanjut usia dan terbagi ke dalam dua kelompok yaitu kelompok pemberian losion vitamin D_3 5000 IU dan kelompok pemberian losion basis. Penilaian dilakukan dengan melihat *overall dry skin score* (ODS), *transepidermal water loss* (TEWL), dan kapasitansi kulit tiap 4 minggu selama 12 minggu. Seluruh kelompok menunjukkan perbaikan pada skor ODS, penurunan nilai TEWL, dan peningkatan nilai kapasitansi kulit pada akhir penilaian dan tidak ditemukan adanya efek samping. Kelompok pemberian losion vitamin D_3 5000 IU memiliki tingkat kelembapan kulit yang paling tinggi dibandingkan dengan kelompok lainnya ($p>0,05$). Kami menyimpulkan bahwa pemberian losion vitamin D_3 5000 IU dapat diberikan secara aman dan dapat memperbaiki hidrasi kulit pada lanjut usia namun tidak lebih efektif dibandingkan dengan losion basis.

Keywords:
dry skin;
elderly;
topical vitamin D_3;
skin hydration;
trial

INTRODUCTION

According to the United Nations World Population Ageing Report, an elderly is someone aged ≥60 yr, and the population will exceed that of young adults by 2050. Dry skin is a common condition in the elderly, with a prevalence of 29.5-58.3%.[1] The exact cause of dry skin in the elderly has not been completely identified, but several intrinsic and extrinsic mechanisms

*corresponding author: danarti@ugm.ac.id

contribute to this issue. A change in keratinocyte proliferation and differentiation, a decrease in skin lipid levels in the epidermis and sebaceous glands, and impaired skin barrier permeability are suggested to be the main causes of dry skin in the elderly. The use of polypharmacy, such as diuretics, anticholesterol, antiandrogen, and cimetidine drugs; the use of strong soaps or cleansers; the use of hot water; and other environmental factors, such as air conditions should also be considered as contributors to dry skin in the elderly. Dry skin is associated with pruritus, which can lead to scratching, secondary infections, and chronic wounds. This situation can certainly interfere with elderly patients' health and quality of life.[1,2]

Vitamin D is an essential fat-soluble vitamin that is synthesized in the skin by exposure to ultraviolet B (UVB) radiation.[3,4] Vitamin D3 is acknowledged to control the proliferation and differentiation of keratinocytes and the formation of the skin permeability barrier. Vitamin D_3 also can improve filaggrin and the natural moisturizing factor (NMF) of the skin. Russell reported that in conditions of low vitamin serum levels, there was a decrease in skin conduction, and topical administration of vitamin D_3 at a dose of 10μg/g cholecalciferol could improve skin conduction, as indicated by an increase of skin hydration.[5] Skin barrier function and skin moisture level can be assessed through clinical evaluation with overall dry skin score (ODS), transepidermal water loss (TEWL) examination, and skin capacitance examination.[6,7] This study was the first to investigate the topical administration of vitamin D_3 with the active ingredient of 7-DHC for dry skin in the elderly in Indonesia.

This study aims to assess the effectiveness of topical supplementation of vitamin D_3 in improving skin hydration in the elderly. This study is expected to enhance clinician understanding of topical administration of vitamin D_3 in improving skin hydration, which can further be used as a therapeutic option in repairing the skin barrier and improving dry skin in the elderly.

MATERIAL AND METHODS

Subjects and design of study

This study was conducted at the Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (FMPHN-UGM) from September to December 2021. This study is a double-blind, randomized controlled trial. Randomization was conducted using the simple randomization method to divide the subjects into two groups. The research subjects were elderly with dry skin who were willing to participate in the study and met the inclusion and exclusion criteria. The inclusion criteria included elderly women and men (aged ≥ 60 yr) in

the Yogyakarta City, subjects diagnosed with clinically dry skin based on overall dry skin scores (ODS) with a minimum score of 1, subjects willing to follow research procedures and sign informed consent, and preferably those who can perform daily activities independently. Subject exclusion criteria were elderly who suffered from skin inflammation at the area where the test material would be applied, elderly who had complaints and needed topical therapy in the test area, and elderly who were incompetent and did not have a representative in giving informed consent.

Procedure

Treatment subjects received topical vitamin D_3 with a form of vitamin D_3 lotion containing 5% 7-DHC equivalent to 5000 IU cholecalciferol, while control subjects received base lotion. The skin hydration level was assessed by measuring dry skin score using ODS, transepidermal water loss (TEWL) using Tewameter®, and skin capacitance using Corneometer®. Side effects were assessed based on subjective assessment using the Safety Assessment Scale criteria.

Week 0 examination was conducted to obtain baseline characteristic data, and then subjects underwent a washout period for one week. During the washout period, subjects would receive the same type of body wash and were not allowed to use other topical preparations. Three fingertip units (FTU) of lotion were applied to the left arm twice daily. After applying the lotion, the subject was asked to bask in the sun for 15 min at maximum. Measurement evaluation was carried out at weeks 4, 8, and 12.

The protocol of this study has obtained an ethical clearance letter from the Medical and Health Research Ethics Committee (MHREC) FMPHN-UGM.

Data analysis

Data analysis was performed using Microsoft Excel and SPSS programs.

RESULTS

The research was conducted on 32 subjects of elderly with dry skin who were evenly divided into two groups. All research subjects were able to complete the research process. Based on the data of research subjects' characteristics, the average age of the subjects in all groups was 70.94 ± 5.53 y.o. Gender distribution in all groups showed more female subjects compared to men, with a proportion of 71.9%. The proportion of elderly with systemic diseases including diabetic mellitus, hypertension, and congestive heart failure was 31.3%. Examination of the basic characteristics of the subjects at week 0 showed no significant mean differences in all variables ($p>0.05$), indicating that the initial data of the two groups were homogeneous.

At the end of the measurement, both groups showed a significant decrease in dry skin score (FIGURE 1) and TEWL value (FIGURE 2). Skin capacitance values in both groups increased at week 12 but were not statistically significant (FIGURE 3). FIGURE 4 shows the comparison of the mean difference of each variable in both groups. The improvement in skin hydration appeared to be more prominent in the vitamin D_3 5000 IU lotion group by 9.35±10.76 a.u compared to the base lotion group by 2.93±7.44 a.u ($p>0.05$). No side effects were found in all subjects of both groups.

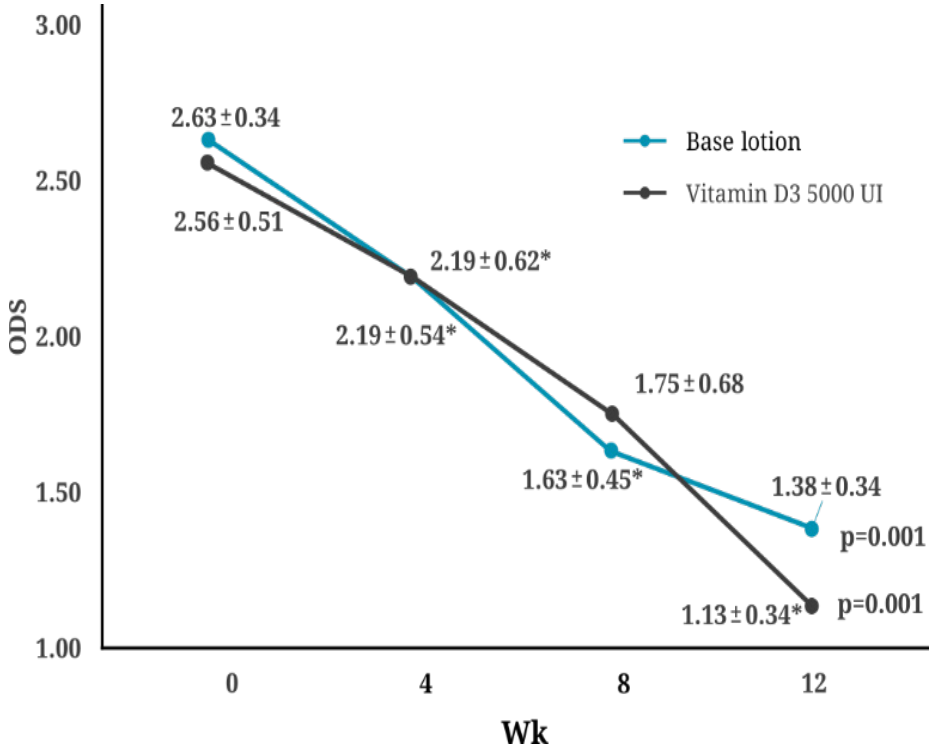

FIGURE 1. The difference in ODS mean scores (week 0 to week 12)

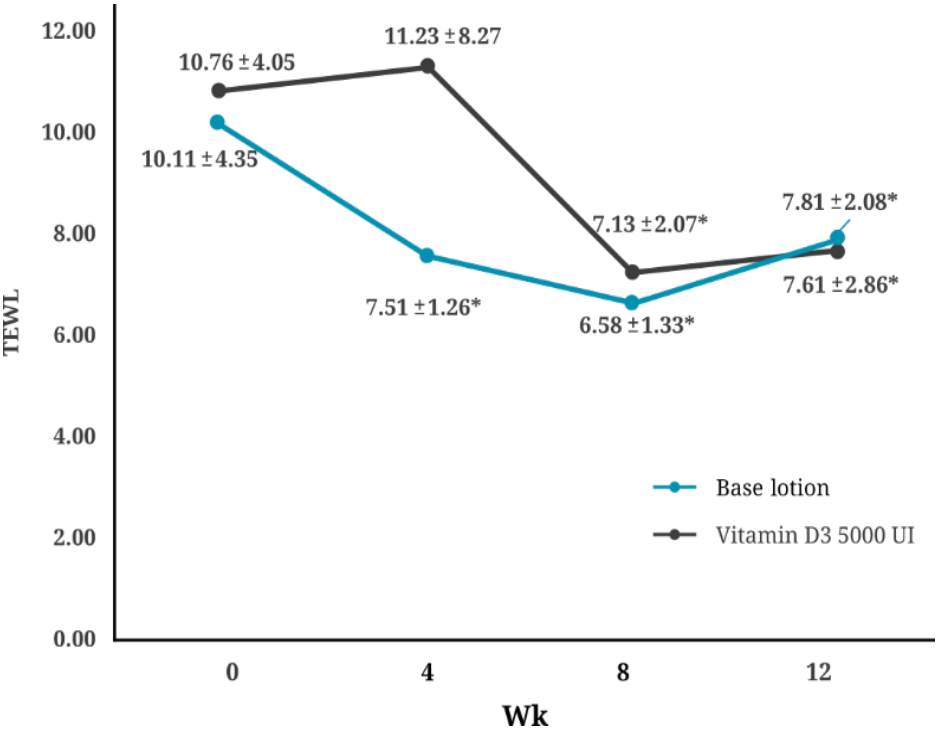

FIGURE 2. The difference in TEWL mean scores (week 0 to week 12)

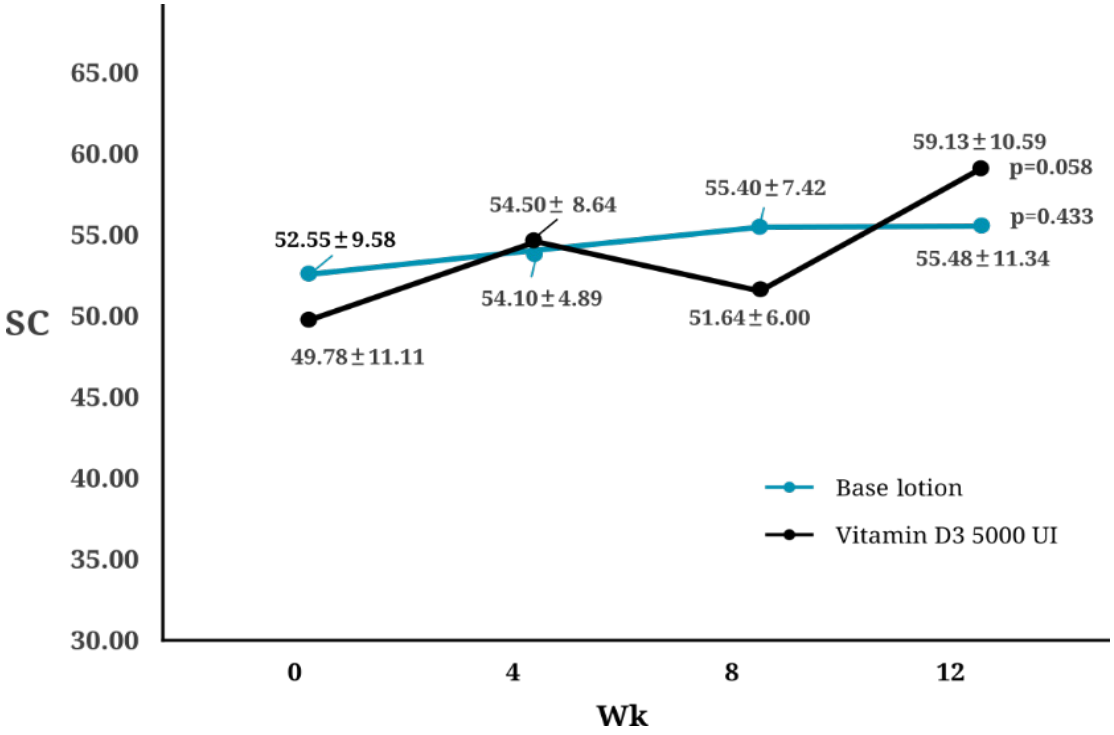

FIGURE 3. The difference in skin capacitance mean scores (week 0 to week 12)

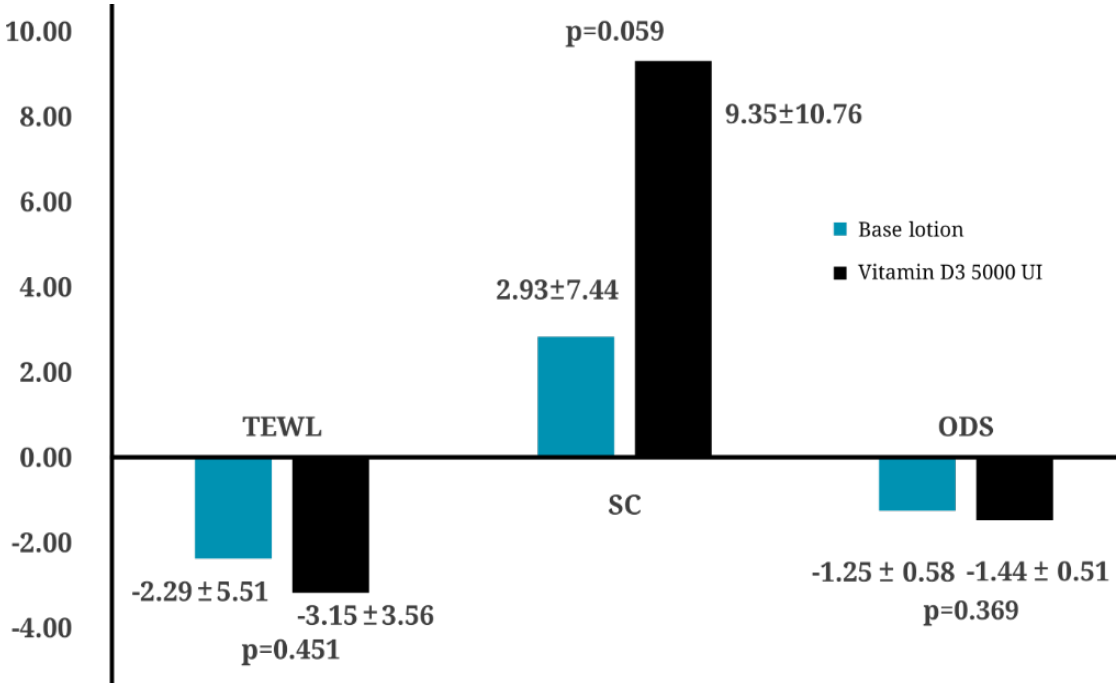

FIGURE 4. The difference in mean changes in TEWL, skin capacitance, and ODS

DISCUSSION

The use of moisturizers is the main therapy for dry skin The target purposes of dry skin treatment include rehydrating the epidermis and improving skin barrier function.[9] The use of moisturizers containing vitamin D_3 for 12 wk was found to be effective in improving skin hydration in the elderly with dry skin. This finding is in line with previous studies on the topical administration of vitamin D_3. Russell reported that there is a link between vitamin serum levels and skin hydration levels. Individuals with lower vitamin serum levels were found to have lower skin hydration levels. Topical supplementation of vitamin D_3 in this study was reported to improve skin hydration and repair dry skin significantly.[5]

Vitamin D_3 in the skin through sun exposure can be converted into its active form, namely 1.25 $(OH)_2D_3$ (calcitriol) with the help of vitamin D-25 hydroxylase (CYP27A) and 25OHD-1-hydroxylase (CYP27B1) enzymes.[10] 1,25 $(OH)_2D_3$ works through the vitamin D receptor (VDR) on keratinocytes.[11] 1,25 $(OH)_2D_3$ has an important role in regulating the proliferation of the basal stratum of the epidermis and triggering keratinocyte differentiation.[12] 1.25(OH)2D3, together with calcium, also plays an important role in increasing the expression of involucrin, transglutaminase, loricrin, and filaggrin and regulates the processing of glucosylceramide long chains that play a role in skin barrier formation.[13]

Aging affects calcitriol production, which drops by 50% due to a decrease in renal function while causing a decrease in calcium absorption by the body. Other effects of aging on vitamin D include a decrease in VDR, a decrease in vitamin D production in the skin, and a deficiency of vitamin D-forming materials. A decrease in the 7-DHC concentration in the epidermis of the elderly led to a 50% decrease in pre-vitamin D_3 formation. Deficiency of substrates or vitamin D-forming materials in the elderly is common. Deficiencies can occur due to poor nutritional intake or lack of sun exposure.[14]

From the study results, it was found that an administration of vitamin D_3 lotion containing 5000 IU was effective in improving the hydration of elderly skin. However, similar results were also found in the base lotion group. It was presumably due to emollient, humectant, and occlusive ingredients in the base lotion. The most concerning complications from topical administration of vitamin D_3 are hypercalcemia and hyperuricemia, but no studies have reported these cases. Hypercalcemia is reported not to occur in patients taking less than 100 g of calcipotriol per week. The most common side effects encountered in topical vitamin D are mild pruritus and irritation, which were not encountered in this study.[15]

Some of the limitations of this study include still involving elderly with a history of chronic diseases and the use of routine medicine because it was difficult to find elderly who were completely healthy or without comorbidities. This condition may also affect the final results of the study. The base lotion also contains emollient, humectant, and occlusive ingredients, so it is better to limit the active ingredients of the base lotion when comparing moisturizers in clinical trials for more precise results.

CONCLUSION

We conclude that the administration of 5000 IU vitamin D_3 lotion is safe to be administered to the elderly and is beneficial in improving dry skin in the elderly. However, the administration of 5000 IU VD3 lotion is not more effective than base lotion.

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Improvement in left ventricle geometry and function after kidney transplantation

Baiq Gerisa Rahmi Faharani[1], Hasanah Mumpuni[1], Yulia Wardhani[2], Metalia Puspitasari[2], Raden Heru Prasanto[2], Iri Kuswadi[2], Anggoro Budi Hartopo[1]*

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia, [2]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

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ABSTRACT

Chronic kidney disease (CKD) is associated with remodeling of the left ventricle (LV), affecting both its geometry and function. Kidney transplantation in patients with stage 5 CKD may lead to improvements in LV remodeling and result in better cardiac function. The aim of the study was to determine changes and improvements in LV geometry and function after kidney transplantation in patients with stage 5 CKD. This was an observational study conducted by collecting secondary data from the Hospital's Kidney Transplantation Registry, Dr. Sardjito General Hospital spanning the years 2017 to 2020. The study employed a comparative design, contrasting the results before and after treatment (kidney transplantation). We compared transthoracic echocardiographic parameters for LV geometry and function before and after kidney transplantation. The evaluation timeframe after kidney transplantation was divided into <12 and ≥12 mo. A total of 27 patients qualified for inclusion in this study. In the <12 mon (n=20) evaluation group, there was a reduction in proportion of LV hypertrophy from 70% to 45%. There was an increase in global LV systolic function (ejection fraction) from 60.1±10.95% to 67.85±6.48% (p=0.014), and a decrease in LV diastolic dysfunction from 45% to 15% (p=0.07). In the ≥12 mon (n=11) evaluation group, there was a decrease in the proportion of LV hypertrophy from 81.8 to 54.5%, an increase in global LV systolic function (ejection fraction) from 57.73±13.07% to 69.36±6.12% (p=0.011), and a decreased LV diastolic dysfunction from 63.6% to 0% (p=0.016). In conclusion, significant changes in LV geometry and function are observed following kidney transplantation, indicating improvements in these parameters. There are improvements in LV systolic function started at <12 mo and in LV diastolic function at ≥12 mo after kidney transplantation.

ABSTRAK

Penyakit ginjal kronis (PGK) dikaitkan dengan remodeling ventrikel kiri (VK), yang mempengaruhi geometri dan fungsinya. Transplantasi ginjal pada pasien dengan PGK stadium 5 dapat menyebabkan perbaikan dalam remodeling ventrikel kiri (VK) dan menghasilkan fungsi jantung yang lebih baik. Tujuan penelitian adalah untuk mengetahui perubahan dan perbaikan geometri dan fungsi VK setelah transplantasi ginjal pada pasien PGK stadium 5. Ini adalah penelitian observasional yang dilakukan dengan mengumpulkan data sekunder dari Registrasi Transplantasi Ginjal Rumah Sakit, RSUP Dr. Sardjito, Yogyakarta selama tahun 2017 hingga 2020. Penelitian ini menggunakan desain komparatif, yang membandingkan hasil sebelum dan sesudah perawatan (transplantasi ginjal). Kami membandingkan parameter ekokardiografi transthorak untuk geometri dan fungsi VK sebelum dan sesudah transplantasi ginjal. Jangka waktu evaluasi setelah transplantasi ginjal dibagi menjadi <12 dan ≥12 bulan. Sebanyak 27 pasien memenuhi syarat untuk diikutsertakan dalam penelitian ini. Pada kelompok evaluasi <12 bulan (n=20), terdapat penurunan proporsi hipertrofi ventrikel kiri dari 70% menjadi 45%. Terdapat peningkatan fungsi sistolik VK global (fraksi ejeksi) dari 60,1±10,95% menjadi 67,85±6,48% (p=0,014), dan penurunan disfungsi diastolik VK dari 45% menjadi 15% (p=0,07). Pada kelompok evaluasi ≥12 bulan (n=11), terjadi penurunan proporsi hipertrofi ventrikel kiri dari 81,8 menjadi 54,5%, peningkatan fungsi sistolik ventrikel kiri global (fraksi ejeksi) dari 57,73±13,07% menjadi 69,36±6,12% (p=0,011), dan penurunan disfungsi diastolik VK dari 63,6% menjadi 0% (p=0,016). Kesimpulannya, perubahan signifikan pada geometri dan fungsi VK diamati setelah transplantasi ginjal, yang menunjukkan perbaikan pada parameter ini. Terdapat perbaikan pada fungsi sistolik VK yang dimulai pada <12 bulan dan fungsi diastolik LV pada ≥12 bulan setelah transplantasi ginjal.

Keywords:
kidney transplantation; left ventricular function; left ventricular geometry; chronic kidney disease; cardiopathy

*corresponding author: a_bhartopo@ugm.ac.id

INTRODUCTION

Cardiovascular complications can manifest at any stage of chronic kidney disease (CKD), irrespective of the glomerular filtration rate (GFR).[1] Left ventricular hypertrophy (LVH) stands as a hallmark of uremic cardiopathy, closely associated with type 4 cardiorenal syndrome or chronic cardiorenal syndrome, a consequence of CKD. Left ventricular hypertrophy arises from chronic pressure or volume overload, resulting in increased cardiac wall pressure.[1] In its early stages, it is deemed an adaptive response to these overloads. Notably, left ventricular diastolic filling disturbances are frequently observed.[2] Subsequently, the remodeling of LV geometry persists, eventually leading to the disruption of left ventricular systolic function.[2]

Stage 5 CKD, also known as end-stage renal disease (ESRD) necessitates kidney replacement therapy. Three modalities are available: hemodialysis, peritoneal dialysis, and kidney transplantation. According to the 2018 Indonesian Renal Registry (IRR) data in the 11th IRR Report, the majority of services provided at dialysis service facilities are hemodialysis (98%), while continuous ambulatory peritoneal dialysis (CAPD) services make up 2%.[3] Furthermore, as much as 11% of CAPD patients have discontinued and transferred to hemodialysis, with kidney transplantation accounting for as much as 1%.[3]

Kidney transplantation is associated with improvements in cardiac structure and function.[4] For patients with stage 5 CKD, kidney transplantation yields positive cardiovascular effects and enhances cardiac function.[5] Left ventricular global function was assessed by measuring the difference between end-diastolic and end-systolic values of a one-dimensional (1D), 2D, or 3D parameter divided by the end-diastolic value.[6] In a previous study, we found that among 15 kidney transplant recipients, left ventricular ejection fraction (LVEF) significantly increased, with a mean improvement of 14.3% after kidney transplantation. Notably, all patients with reduced ejection fraction exhibited an increase in LVEF, with a mean improvement of 37%. The proportion of patients with diastolic dysfunction decreased significantly.[7] In this study, we expand and confirm these findings by including more subjects. Our aim is to investigate the impact of kidney transplantation on left ventricle geometry and function, which will be assessed before and after kidney transplantation using transthoracic echocardiography (TTE).

MATERIAL AND METHODS

Design and subjects

This is an observational study conducted by collecting secondary data from the Hospital Kidney Transplantation Registry of Dr. Sardjito General Hospital, Yogyakarta. The study used a comparative design comparing the before and after treatment (kidney transplantation) result. This study was performed after obtaining ethical clearance from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada Yogyakarta, Indonesia (No: KE/FK/0804/EC/2021).

This study enrolled subjects who were kidney transplant recipients at Dr. Sardjito General Hospital, from August 2017 until December 2020. The inclusion criteria were patients with 1) aged >18 yr; 2) underwent kidney transplantation and recorded in the kidney transplant registry of our hospital; 3) underwent TTE examination within 3 mo before transplantation; and 4) underwent TTE examination after transplantation. The exclusion criteria were the incomplete data required for primary outcome analysis, i.e. TTE data.

Procedures

Trained sonographers from the echocardiography division conducted the TTE using one of the echocardiography machines: Vivid 7 (GE Vingmed, Norway, M4s transducer), Vivid 6 (GE Vingmed, Norway, M4s transducer), T8 (GE Vingmed, China, 3Sc transducer), Epiq 7 (Phillips, USA, X5-1 transducer), or E95 (GE Vingmed, Norway, M5Sc transducer). The baseline TTE was performed within 3 mo before kidney transplantation, while the evaluation TTE was conducted after the transplantation. Intraobserver and interobserver validity tests had been previously carried out.[8] The TTE parameters recorded during the examination were based on standard parameters recommended by the Indonesian Society of Echocardiography, following international guideline.[2]

Measurements

The left ventricular geometry was measured based on the M-mode linear method. It was obtained from the parasternal long axis approach and perpendicular to the long axis of the left ventricle, and were measured at the height of the leaflet tip of the mitral valve during the end diastolic phase. The left ventricle mass index (LVMi) and relative wall thickness (RWT) values were obtained, and categorized into 1) normal (male: LVMi ≤115 g/m^2, RWT ≤0.42; female: ≤95 g/m^2, RWT ≤0.42); 2) left ventricle concentric remodeling (male: LVMi ≤115 g/m^2, RWT >0.42; female: ≤95 g/m^2, RWT >0.42); 3) left ventricle concentric hypertrophy (male: LVMi >115 g/m^2, RWT >0.42; female: >95 g/m^2, RWT >0.42); or 4) left ventricle eccentric hypertrophy (male: LVMi >115 g/m^2, RWT ≤0.42; female: >95 g/m^2, RWT ≤0.42).[2] The left atrial volume index (LAVI) was measured based on 2D biplane method.[2]

The left ventricular functions investigated were systolic and diastolic functions. Assessment of systolic function was based on 2D biplane or linear M-mode method. The 2D biplane method was obtained from the modified Simpson method approach. The left ventricular systolic dysfunction was determined as LVEF ≤50%. Assessment of diastolic function was done based on 4-variable methods using pulse wave Doppler for assessment of E, A, e' wave velocity and continuous wave Doppler for tricuspid regurgitant jet velocity assessment.[2]

Statistical analysis

Statistical analysis using SPSS software v.26 (IBM Corp., USA). The comparison and changes of TTE parameters, as numerical data, before and after kidney transplantation were tested by paired t-tests and Wilcoxon tests, where applicable. The Kolmogorov-Smirnov or Shapiro-Wilk tests was conducted to determine the distribution of numerical data. The categorical data were compared by McNemar test. The subjects were divided into groups based on the period of TTE evaluation performed at follow-up, namely the evaluation group <12 mo (n=20 subjects) and the evaluation group ≥12 mo (n=11 subjects). The p value <0.05 was set as a guide for statistical significance.

RESULTS

Subjects Characteristics

A total of 27 subjects qualified for this study. The mean age among these subjects was 37.67±12.35 y.o., with male subjects comprising the highest proportion (n=18, 66.7%). The mean duration of hemodialysis was 16.0 (range: 4.0-84.0) months. Comorbidities included hypertension (n=17, 63.0%) and diabetes mellitus (n=5, 18.5%). TABLE 1 shows the subjects characteristics.

The changes in left ventricular

geometry, as well as systolic and diastolic functions before and after kidney transplantation, are presented in TABLE 2. Significant improvements were observed in left ventricle geometry, with a reduction in the proportion of LV eccentric hypertrophy, transitioning towards milder LV remodeling. Both LV systolic and diastolic functions exhibited improvement following kidney transplantation. Notably, LVEF increased post-translation. Additionally, LAVI demonstrated improvement after kidney transplantation. Laboratory parameters also exhibited positive changes, with hemoglobin levels and creatinine levels notably improving.

TABLE 3 presents the analysis of the changes in LV geometry, systolic and diastolic functions before and during two different post-kidney transplantation follow-up periods, namely <12 mo and ≥12 mo. Twenty subjects were observed during the <12 mo follow-up period after kidney transplantation. LVEF significantly increased after kidney transplantation (p=0.014). Four subjects with LV systolic dysfunction before kidney transplantation exhibited improved function after transplantation. Eight subjects with diastolic dysfunction prior to kidney transplantation showed better function after transplantation, with only one subject still presenting diastolic dysfunction. Within the <12 mo follow-up period after kidney transplantation, LV geometry improved, as indicated by a reduction in LV eccentric hypertrophy and an increase in LV concentric remodeling.

Eleven subjects were observed until ≥12 mo follow-up. The LVEF was significantly increased (p=0.011). Three subjects with LV systolic dysfunction before kidney transplantation had improved LV systolic function after transplantation. Seven subjects with diastolic dysfunction before kidney transplantation, all had improved after transplantation. The LV geometry shifted into improvement in ≥12 mo follow-up after kidney transplantation, indicated by reduced LV eccentric hypertrophy and increased LV concentric remodeling.

Before kidney transplantation, there were two subjects with LVEF <40%, due to global hypokinetic, and within <12 mo follow-up after kidney transplantation, the LVEF improved into normal value. Two other subjects with LVEF <40%, one with global hypokinetic and another with segmental hypokinetic, were evaluated ≥12 mo follow-up and became normal ejection fraction (FIGURE 1). These four subjects with LVEF <40% were males, aged between 26 to 52 yr, had hemodialysis duration from 13 to 84 mo. All had hypertension and none had diabetes mellitus.

TABLE 1. The comparison of the characteristics of subjects during pre-and post-kidney transplantation periods

Characteristics	Pre-transplantation (n=27)	Post-transplantation (n=27)	p
Age (mean ± SD yr)	37.67±12.35	37.67±12.35	NA
Males [n (%)]	18 (66.7)	18 (66.7)	NA
Hemodialysis duration (mo)*	16.0 (4.0-84.0)	16.0 (4.0-84.0)	NA
Hypertension [n (%)]	17.0 (63.0)	17.0 (63.0)	NA
Use of antihypertension [n (%)]	17 (100)	12 (70.6)	0.063
Diabetes mellitus [n (%)]	5 (18.5)	5 (18.5)	NA

*Data were expressed as median (range value).

TABLE 2. The comparison of the changes in left ventricular geometry and functions during pre- and post-kidney transplantation periods

Characteristics	Pre-transplantation (n=27)	Post-transplantation (n=27)	p
LV Geometry [n (%)]			0.038
• Normal geometry	6 (22.2)	5 (18.5)	
• LV eccentric hypertrophy	10 (37.0)	0 (0)	
• LV concentric hypertrophy	10 (37.0)	12 (44.4)	
• LV concentric remodeling	1 (3.7)	10 (37.0)	
LV ejection fraction (mean ± SD %)	59.22±12.3	69.26±5.95	<0.001
LV systolic dysfunction [n (%)]	7 (25.9)	0 (0.0)	0.016
LV diastolic dysfunction [n (%)]*	12 (44.4)	0 (0.0)	0.002
LAVI [med (min–max) mL/m^2]	39.0 (16.0-82.0)	24.0 (14.0-51.0)	<0.001
LVIDd (mean ± SD mm)	51.85±6.7	43.52±5.89	<0.001
Hemoglobin (mean ± SD g/dL)	9.78±1.85	14.06±2.08	<0.001
Urea nitrogen [med (min-max)mg/dL]*	11.8 (4.2-44.6)	18.2 (5.4-50.9)	0.011
Creatinine [med (min-max) mg/dL]*	2.91 (1.30-6.13)	1.28 (0.76-3.09)	<0.001

*1 subject can not be evaluated; LV: left ventricle; LAVI: left atrial volume index; LVIDd: left ventricle internal diameter end diastole; NA: not applicable; SD: standard deviation; med: median; min: minimum; max: maximum

TABLE 3. The changes in LV geometry and functions between pre- and post-kidney transplantation in the follow-up evaluation period of <12 and ≥ 12 mo

Evaluation periods/Parameters	Pre-transplantation	Post-transplantation	p
Evaluation periods of < 12 mo (n=20)			
LV ejection fraction (mean ± SD %)	60.1±10.95	67.85±6.48	0.014
LV systolic dysfunction [n (%)]	4 (20)	0 (0)	0.125
LV geometry [n (%)]			
• Normal	5 (25.0)	3 (15.0)	0.135
• LV eccentric hypertrophy	6 (30.0)	0 (0.0)	
• LV concentric hypertrophy	8 (40.0)	9 (45.0)	
• LV concentric remodeling	1 (5.0)	8 (40.0)	
LV diastolic function [n (%)]*			
• Normal	11 (55.0)	17 (85.0)	0.061
• Indeterminate	0 (0.0)	1 (5.0)	
• Diastolic dysfunction	8 (40.0)	1 (5.0)	
Evaluation periods of ≥12 mo (n=11)			
LV ejection fraction [mean ± SD %]	57.73±13.07	69.36±6.12	0.011
LV systolic dysfunction [n (%)]	3 (27.3)	0 (0)	0.250
LV geometry [n (%)]*			
• Normal	2 (18.2)	3 (27.3)	0.116
• LV eccentric hypertrophy	5 (45.5)	0 (0.0)	
• LV concentric hypertrophy	4 (36.4)	6 (54.4)	
• LV concentric remodeling	0 (0.0)	2 (18.2)	
LV diastolic function [n (%)]			
• Normal	4 (36.4)	11 (100.0)	0.016
• Diastolic dysfunction	7 (63.6)	0 (0.0)	

*1 subject could not be evaluated, SD: standard deviation.

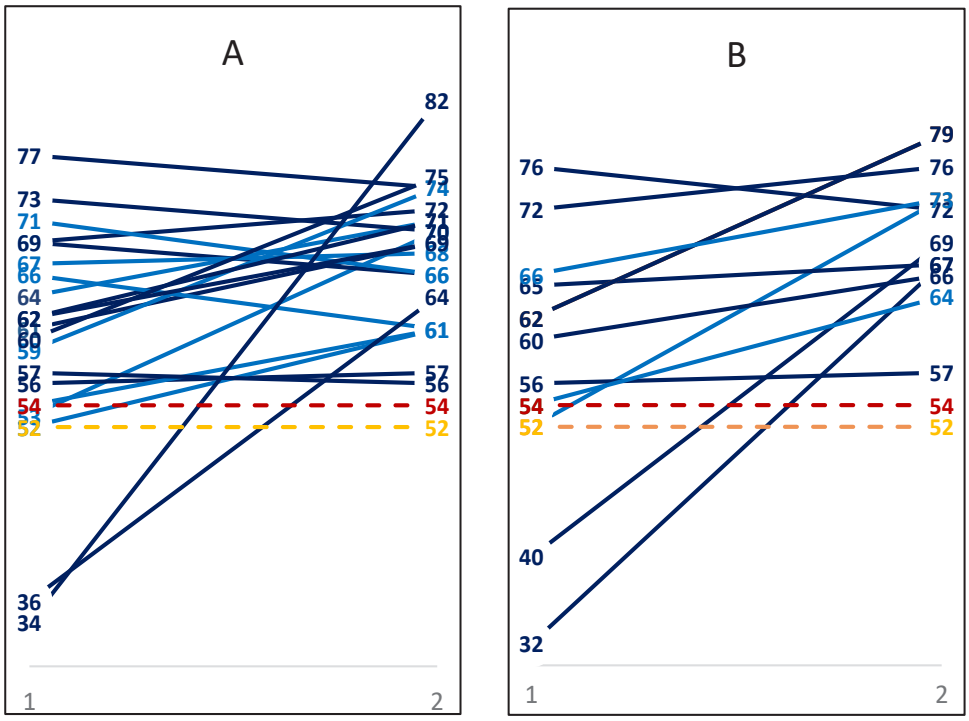

FIGURE 1. The graph of the changes in LV ejection fraction. A) The evaluation within <12 mo follow-up post-kidney transplantation (n=20). B) The evaluation ≥12 mo follow-up post-kidney transplantation (n=11). 1) Pre-kidney transplantation; 2. Post-kidney transplantation. Dark blue line: males. Light blue Line: females. Red dotted line: female LV ejection fraction normal limit. Yellow dotted line: male LV ejection fraction normal limit.

TABLE 4 shows the comparison of TTE parameters, diagnosis and laboratory results between before and after kidney transplantation within evaluation of <12 mo follow-up and ≥12 mo follow-up periods. In subjects with evaluation <12 mo follow-up, there were significant changes in most of TTE parameters namely RWT, LVMi, LAVI, LV diameters, LV ejection fraction, E/A ratio and tricuspid regurgitation velocity. These significant changes were also observed in subjects with ≥12 mo follow-up, except for RWT and E/A ratio. The proportion of subjects with LV hypertrophy tended to decrease after kidney transplantation in both evaluation groups. Subjects with systolic and diastolic dysfunctions were improved after kidney transplantation in both evaluation groups. There were also significant changes in laboratory values after kidney transplantation.

TABLE 4. The TTE parameters, diagnosis and laboratory results between pre- and post-kidney transplantation in evaluation period of <12 and ≥12 mo follow-up

Parameters	<12 mo follow-up (n=20)		p	≥12 mo follow-up (n=11)		p
	Pre-transplantation	Post-transplantation		Pre-transplantation	Post-transplantation	
TTE parameters						
• Relative wall thickness [med (min – max)]	0.42 (0.32-0.97)	0.5 (0.39-1.03)	0.030	0.38 (0.34-0.97)	0.47 (0.33-0.67)	0.328
• LV mass index (mean ± SD g/m^2)	154.0±61.0	116.0±36.9	0.004	172.4±61.9	96.6±28.7	0.006
• LAVI (mean ± SD mL/m^2)	38.0 (16.0-82.0)	22.5 (12.0-51.0)	0.001	51.9±17.7	25.0±7.1	<0.001
• LVIDd (mean ± SD mm)	50.95±7.2	43.4±5.56	<0.001	53.91±7.44	43.73±6.21	<0.001
• LV ejection fraction (mean ± SD %)	60.1±10.95	67.85±6.48	0.014	57.73±13.1	69.36±6.12	0.011
• E/A ratio [median (min – max)]	1.2 (0.78-3.10)	1.03 (0.6-3.0)	0.018	1.3 (0.9-92.0)	0.79 (0.0-9.0)	0.075
• TR velocity [median (min – max) m/s]	1.2 (0.0-4.79)	0.0 (0.0-2.76)	0.028	2.74 (0.0-3.96)	0.0 (0.0-2.45)	0.018
Diagnosis						
• LV hypertrophy [n (%)]	14 (70.0)	9 (45.0)	0.125	9 (81.8)	6 (54.5)	0.375
• Systolic dysfunction [n (%)]	4 (20.0)	0 (0.0)	0.125	3 (27.3)	0 (0.0)	0.250
• Diastolic dysfunction [n (%)]	9 (45.0)	3 (15.0)	0.070	7 (63.6)	0 (0.0)	0.016
Laboratory results						
• Hemoglobin (mean ± SD g/dL)	9.8±1.68	13.33±2.27	<0.001	9.6±2.1	14.66±2.01	<0.001
• Urea nitrogen (mean ± SD mg/dL)	14.35 (4.2-44.6)	18.8 (10.4-50.9)	0.121	8.5 (4.2-23.5)	18.4 (5.4-30.9)	0.021
• Creatinine (mean ± SD mg/dL)	3.11 (1.30-6.13)	1.13 (0.76-3.09)	<0.001	2.57±0.85	1.45±0.42	0.001

SD: standard deviation; med: median; min: minimum; max: maximum; TEE: transthoracal echocardiography; LV: Left ventricle; LAVI: Left atrial volume index, LVIDd: Left ventricle internal diameter end diastole; TR: tricuspid regurgitation.

DISCUSSION

The results of our study indicated that there were improvements in LV geometry, LV systolic and LV diastolic function after kidney transplantation. The improvement in LV geometry tended to occur within one year after kidney transplantation and continued after one-year follow-up. The proportion of LV hypertrophy tended to reduce. The LV systolic dysfunction improved in one-year evaluation and more than one-year follow-up. The increase in LVEF was significantly raised to within the normal range subjects with initially reduced LVEF. Improved LV diastolic function was observed in the one-year evaluation and continued to be significant one year after kidney transplantation.

Previous studies have indicated changes in LV structure and geometry based on echocardiographic examinations in patients with stage-V-CKD at the initiation of hemodialysis therapy.[9] In patients who underwent kidney transplantation, the changes in LV structure and geometry were observed in previous studies. The comparison of echocardiographic results in the

before kidney transplantation and after kidney transplantation periods showed significant improvement changes.[10] Our study indicated similar findings such that the LV geometry and functions corrected significantly after kidney transplantation among stage V CKD patients.

Our study demonstrated significant improvements in LV systolic function within one year, which were sustained in the one-year evaluation. These favorable changes in systolic function after kidney transplantation at 6 and 12 mo were observed by other previous study.[5] The kidney transplantation can be performed safely in stage 5 CKD patients with decreased LV ejection fraction, advanced heart failure, and without induced ischemia.[11] Our study indicated that subjects with LV ejection fraction <40% had returned into normal ejection fraction after kidney transplantation. Improved global systolic function after kidney transplantation is associated with a reduction in excessive blood flow (preload), resulting in enhanced left ventricular inotropic function.[12] The duration of hemodialysis before kidney transplantation is a significant factor that predicts the normalization of LVEF.[11]

The analysis of LV diastolic function showed a significant improvement after one year of kidney transplantation, with the trend toward improvement within one-year follow-up. In the previous study, the diastolic dysfunction did not change significantly after 12 mo of kidney transplantation.[13] This is associated with pathological changes in myocardial anatomy, such as myocardial calcification or fibrosis, which may lead to a lack of improvement in the diastolic index after kidney transplantation.[13] The worsening of LV diastolic function may be attributed to the use of cyclosporine post-transplantation and inadequate blood pressure control.[12]

There was a trend toward the resolution of LV hypertrophy after kidney transplantation, both within the first year and in the follow-up after one yr. The non-significant decrease in LV hypertrophy may be related to the persistence of hypertension that occurs among subjects. We observed the persistence of hypertension after kidney transplantation, with as many as 70.6% of hypertensive subjects continuing to consume anti-hypertensive therapy. It is possible that the persistence of hypertension was due to hypertension being the primary comorbid condition in the subjects, or another possibility of LV hypertrophy associated with treatment using calcineurin inhibitors and steroids. Calcineurin inhibitors and steroids may induce hypertension. All subjects in our study used calcineurin inhibitor (tacrolimus) and steroids as immunosuppressant therapies.

The results of our study showed different findings from other previous studies, which found significant improvement in LV geometry after kidney transplantation. Successful kidney transplantation improves some risk factors for LV hypertrophy such as uremia, anemia, and hyperparathyroidism, but other factors such as patent arteriovenous fistula, dyslipidemia, and hypertension may persist or even worsen after kidney transplantation. Immunosuppressive drugs, such as calcineurin inhibitors, especially cyclosporine and steroids that have the side effect of hypertension play an important role in the development or persistence of LV hypertrophy after kidney transplantation.[10] The presence of an arteriovenous fistula reduces peripheral resistance, thereby creating a hyperkinetic circulation, which increases heart rate and stroke volume index.[12] Changes in LV geometry have been associated with improved blood pressure control, reflecting the impact of afterload on left ventricular remodeling.[2] Our study revealed a wide range of ages among participants; however, age did not appear to affect the outcome of

kidney transplantation.

Uremic toxins in plasma have negative inotropic and chronotropic potential[14] and prolonged exposure to these uremic toxins can cause myocyte fibrosis and death.[15,16] These reasons may suggest that the duration of dialysis can affect changes in diastolic function. Prolonged exposure to uremic toxins has been shown to affect myocardial contractility so that the possibility of improvement in systolic function can also be affected by the duration of dialysis.[17,18] In our study, the mean duration of hemodialysis before kidney transplantation procedure was 16.0 mo.

The kidney transplant graft dysfunction and sustained high blood pressure may contribute to the lack of improvement in LV hypertrophy and other cardiovascular risk factors, such as increased extracellular volume, electrolyte abnormalities, malnutrition, anemia, and uremic toxins, after kidney transplantation.[13] Systolic blood pressure was associated with LV mass and LV mass index at 12 mo after kidney transplantation.[13] There was a significant reduction in LV hypertrophy after kidney transplantation. One explanation for this effect is the possible decrease in systolic blood pressure and improvement in kidney function after kidney transplantation. This notion demonstrates the importance of graft function in the development of LV hypertrophy after kidney transplantation.[13] Insulin resistance, metabolic syndrome, and type 2 diabetes mellitus are associated with increased LV mass, RWT, and diastolic dysfunction.[18] Patients with diabetes mellitus also tend to have decreased systolic function.[12,18] Therefore, the role of comorbidities is also an important factor affecting the LV geometry and function among kidney transplant patients.

There were several limitations identified in this study. First, the small number of subjects from a single center needed to be corroborated by a larger number of study subjects from a multicenter national registry. Two, the relatively short period of observation and follow-up due to the nature of study design needed to be corroborated with a longer and continuous evaluation by using a prospective cohort design. Three, the adequacy of hemodialysis before and technical difficulties during kidney transplantation procedure were not reported in detail in this study.

CONCLUSION

The LV geometry, LV systolic and LV diastolic functions improve after kidney transplantation. The improved LV geometry tends to occur within one year after kidney transplantation and continues after one year follow-up. The LV systolic dysfunction improved in one year evaluation and more than one year follow-up. The LVEF fraction increases significantly even in those with LVEF <40%. The LV diastolic function significantly recovers after one year after kidney transplantation.

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The accuracy of fine needle aspiration biopsy (FNAB) in diagnosing musculoskeletal lesion

Auliya Suluk Brilliant Sumpono[1,4], Junaedy Yunus[2], Yeshua Putra Krisnugraha[3], Ery Kus Dwianingsih[1,4*]

[1]Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Department of Anatomy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [3]Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [4]Dr. Sardjito General Hospital, Yogyakarta, Indonesia

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ABSTRACT

Fine needle aspiration biopsy (FNAB) is a relatively non-invasive diagnosis of musculoskeletal lesions that is very challenging in some musculoskeletal cases. This study aimed to evaluate the diagnostic utility of FNAB in musculoskeletal lesions. This was a retrospective cross-sectional study involving 180 musculoskeletal patients who underwent FNAB procedure, with or without ultrasound-guided in the Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta between 2018 and 2021. The obtained data were then statistically analyzed for sensitivity, specificity, and accuracy. Of 180 cases, 90 (50%) were confirmed with histopathology examination. Further analysis revealed that 33 cases were confirmed positive, 45 patients were true negative, 2 cases were false positive, and 10 were cases false negative. The overall diagnostic sensitivity, specificity, and accuracy of FNAB in musculoskeletal lesions were 76.8, 95.7, and 83%, respectively. FNAB can lead to misinterpretation in cases that show similar morphologic features. Therefore, clinical information and imaging results are necessary to be correlated. In conclusion, FNAB is an efficient and effective technique for early diagnosis in musculoskeletal cases. FNAB can be used to establish the diagnosis of an inoperable tumor because of its high accuracy.

ABSTRACT

Biopsi aspirasi jarum halus (AJH) merupakan metode relatif non-invasif untuk mendiagnosis lesi musculoskeletal yang cukup sulit dilakukan pada beberapa kasus muskuloskeletal. Penelitian ini bertujuan mengevaluasi nilai diagnostik AJH pada lesi muskuloskeletal. Penelitian menggunakan rancangan potong lintang retrospektif pada 180 kasus muskuloskeletal yang menjalani prosedur AJH, dengan atau tanpa panduan USG, di Departemen Anatomi, Fakultas Kedokteran, Kesehatan Masyarakat, Keperawatan, Universitas Gadjah Mada/ RSUP Dr. Sardjito, Yogyakarta antara tahun 2018 dan 2021. Data yang diperoleh dianalisis secara statistik untuk sensitivitas, spesifisitas, dan akurasinya. Dari 180 kasus, terdapat 90 kasus (50%) yang terkonfirmasi melalui pemeriksaan histopatologi. Analisis lebih lanjut menunjukkan bahwa 33 kasus benar-benar positif, 45 kasus benar-benar negatif, 2 kasus positif palsu, dan 10 kasus negatif palsu. Sensitivitas, spesifisitas, dan akurasi diagnostik AJH pada lesi musculoskeletal berturut-turut adalah 76,8, 95,7, dan 83%. Aspirasi jarum halus dapat menyebabkan misinterpretasi pada kasus yang menunjukkan ciri morfologi serupa. Oleh karena itu, perlu dilakukannya korelasi antara informasi klinis dan hasil radiologis. Dapat disimpulkan, AJH merupakan teknik yang efisien dan efektif untuk mendapatkan diagnosis dini pada kasus muskuloskeletal. Aspirasi jarum halus dapat digunakan sebagai pilihan untuk menegakkan diagnosis jika terjadi tumor yang tidak dapat dioperasi karena akurasinya yang tinggi.

Keywords:
FNAB;
cytology;
musculoskeletal lesion;
accuracy

*corresponding author: ery_malueka@ugm.ac.id

INTRODUCTION

Open biopsy procedure has been the gold standard for diagnosing musculoskeletal cases. This procedure has high accuracy, however it has several disadvantages, such as an increased risk of infection, longer length of hospital stays, and the risk of the tumor attaching to surrounding tissue or vessel.[1] Fine needle aspiration biopsy (FNAB) has been used extensively in several organs for early diagnosis, such as breast, lung, and thyroid. Fine needle aspiration biopsy is considered a fast, easy, and affordable method to obtain a diagnosis.[2] Good sampling triage by experienced pathologists, ultrasound-guided technique, and sufficient clinical information of patients may contribute to higher sensitivity and specificity in FNAB.[3]

Studies showed that FNAB can accurately diagnose musculoskeletal lesions with an accuracy as high as 81-97%.[4,5] However, a systematic review and meta-analysis study conducted by Chambers *et al.*[6] reported that FNAB provides higher accuracy for benign bone lesions compared to malignant ones, but definitively diagnoses soft tissue lesions more consistently. Therefore, it is recommended to use FNAB more frequently in the diagnostic workup of bone and soft tissue lesions to minimize invasive procedures for patients.

In Indonesia, data and research on the utility of FNAB in diagnosing musculoskeletal lesions are still limited. Additionally, selecting the appropriate biopsy technique in musculoskeletal cases is complicated and often leads to diagnostic errors. This study aimed to evaluate the accuracy of FNAB in musculoskeletal cases that often can be falsely negative and positive in Dr. Sardjito General Hospital, Yogyakarta, Indonesia.

MATERIALS AND METHODS

Subjects

Fine needle aspiration biopsy cases of musculoskeletal lesions, with or without ultrasound-guided (USG), were collected retrospectively from the Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia, from 2018 until 2020. The study included only cases with confirmed histopathology and complete data on demographic, tumor location, and histopathological subtype. Cases with incomplete data and different histopathology locations from FNAB locations were excluded. This study was approved by the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (reference number: KE/FK/0878/EC/2023).

Protocol

Fine needle aspiration biopsies were performed, both with and without USG guidance. The cytopathology finding from FNAB was considered to be the independent variable, while the histopathological result from excision and biopsy was the dependent variable. Two experienced pathologists blindly examined and documented the samples to avoid potential bias.

Statistical analysis

Data were presented in percentage, and the diagnostic analysis was performed using a 2x2 table to determine the sensitivity, specificity, and accuracy of FNAB in musculoskeletal cases.

RESULTS

Of 180 cases of FNAB in the musculoskeletal lesion, 90 (50%) met the study's criteria. Of these 90 cases, 22 cases were from 2018, 1 patient was from 2019, and 42 cases were from 2020. TABLE 1 presents general subject characteristics based on gender and age. Thirty-seven subjects were male (41.1%), and 53 were female (58.9%). The youngest subject was 6 y.o., while the eldest was 94 y.o.

The data about the predilection of musculoskeletal lesions is shown in TABLE 2. The highest incidence was presented in the 41 to 60 y.o. group (34.5%). The most common location for musculoskeletal lesions was the femur in 20 cases (22.2%), followed by the tibia in 9 patients (10%), genu in 8 cases (8.9%), pedis in 7 cases (7.8%), meanwhile cruris and ulna in 5 cases (5.7%).

TABLE 1. Subject characteristics based on gender and age group (2018 – 2021)

Characteristic	Frequency	%
Gender		
• Male	37	41.1
• Female	53	58.9
Age		
• 0-20	28	31.1
• 21-40	21	23.3
• 41-60	31	34.5
• >60	10	11.1

TABLE 2. The predilection of the musculoskeletal lesion (2018 – 2021)

Predilection	Frequency	%
Sternoclavicular	1	1.1
Ankle	3	3.3
Antebrachia	2	2.2
Bone marrow	2	2.2
Cruris	5	5.7
Chest wall	3	3.3
Digit pedis	1	1.1
Elbow	1	1.1
Femur	20	22.2
Forearm	3	3.3
Fibula	1	1.1
Genu	8	8.9
Gluteus	3	3.3
Humerus	3	3.3
Lumbar	1	1.1
Mandibula	2	2.2
Manus	4	4.5
Maxilla	3	3.3
Pedis	7	7.8
Pelvis	2	2.2
Scapula	1	1.1
Tibia	9	10
Ulna	5	5.7

Fine needle aspiration biopsy cases confirmed with the histopathological result are presented in TABLE 3. Diagnostic analysis of 90 patients showed concordance findings of malignant results in FNAB and histopathological examination in 33 cases (36.7%). The concordance benign result of FNAB and histopathological examination was observed in 45 patients (50%). However, there was a discrepancy between malignant results in FNAB and benign results in a histopathological examination in 2 cases (2.2%). Lastly, 10 patients (11.1%) showed benign results in FNAB. Meanwhile, the histopathological findings revealed malignant results.

The diagnostic value was calculated based on data in TABLE 4. The sensitivity of FNAB in musculoskeletal cases was 76.8%. Meanwhile, the specificity was 95.7%. The positive predictive value (PPV) was 94.3%. Meanwhile, negative predictive value (NPV) was 81.8%. In this study, the accuracy of FNAB in musculoskeletal cases was 83%.

The summary of the histopathology result of all cases is shown in TABLE 5. In this study, most cases of the malignant musculoskeletal lesion were osteosarcoma; 8 cases were conventional osteosarcoma without a specific subtype, 2 cases were conventional osteoblastic type osteosarcoma, 2 cases were conventional giant cell-rich type osteosarcoma, 1 case was epithelioid type osteosarcoma and 1 case with telangiectatic osteosarcoma. Other malignant cases were non-Hodgkin lymphoma (NHL) in 5 cases and chondrosarcoma in 5 cases. In benign musculoskeletal lesions, the most common cause was Giant Cell Tumor (GCT) in 12 cases, followed by nonspecific benign lesions in 5 cases and hemangiomas in 4 cases. FIGURE 1 shows a representative image result of FNAB.

TABLE 3. FNAB finding compared to histopathology result

		Histopathology		Total
		Malignant	Benign	
FNAB	Malignant	33	2	35
	Benign	10	45	55

Note: FNAB: fine needle aspiration biopsy

TABLE 4. Sensitivity, specificity, PPV, NPV, and the accuracy of FNAB compared to histopathology

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
FNAB in musculoskeletal lesion	76.8	95.7	94.3	81.8	83.0

Note: FNAB: fine needle aspiration biopsy; PPV: positive predictive value; NPV: the negative predictive value

TABLE 5. Summary of the histopathology result

Malignant	Frequency (n)	Benign	Frequency (n)
Conventional osteosarcoma, unspecific type	8	Giant cell tumor (GCT)	12
Conventional osteosarcoma, osteoblastic type	2	Benign nonspecific	5
Conventional osteosarcoma, giant cell-rich type	2	Hemangioma	4
Conventional osteosarcoma, fibroblastic type	1	Osteomyelitis	3
Osteosarcoma epithelioid type	1	Callus	2
Osteosarcoma, telangiectatic type	1	Aneurysmal bone cyst	2
Chondrosarcoma	5	Fibrous dysplasia	2
Non-Hodgkin lymphoma (NHL)	5	Benign fibrous histiocytoma	1
Metastatic breast adenocarcinoma	3	Benign odontogenic cyst	1
Metastatic papillary thyroid carcinoma	2	Neurofibroma	1
Small round blue cell tumor	2	Osteomalacia (Rickets)	1
Metastasis parathyroid carcinoma	1	Suppurative inflammation with cholesterol ester granuloma	1
Myxofibrosarcoma	1	Rheumatoid nodule	1
Myxoid spindle cell sarcoma	1	Simple bone cyst	1
Rhabdomyosarcoma	1	Chronic Synovitis	1
Classic Adamantinoma	1	Chromoblastomycosis	1
Adamantinoma with squamous differentiation	1	Ganglion cyst	1
Liposarcoma	1	Gout arthritis	1
Malignant germ cell tumor	1	Epidermoid cyst	1
Plasmacytoma	1	Lipoma	1
Rhabdomyosarcoma	1	Myofibroma	1
Undifferentiated pleomorphic sarcoma	1	Neurofibroma	1
		Pigmented villonodular synovitis.	1
		Synovial cyst	1

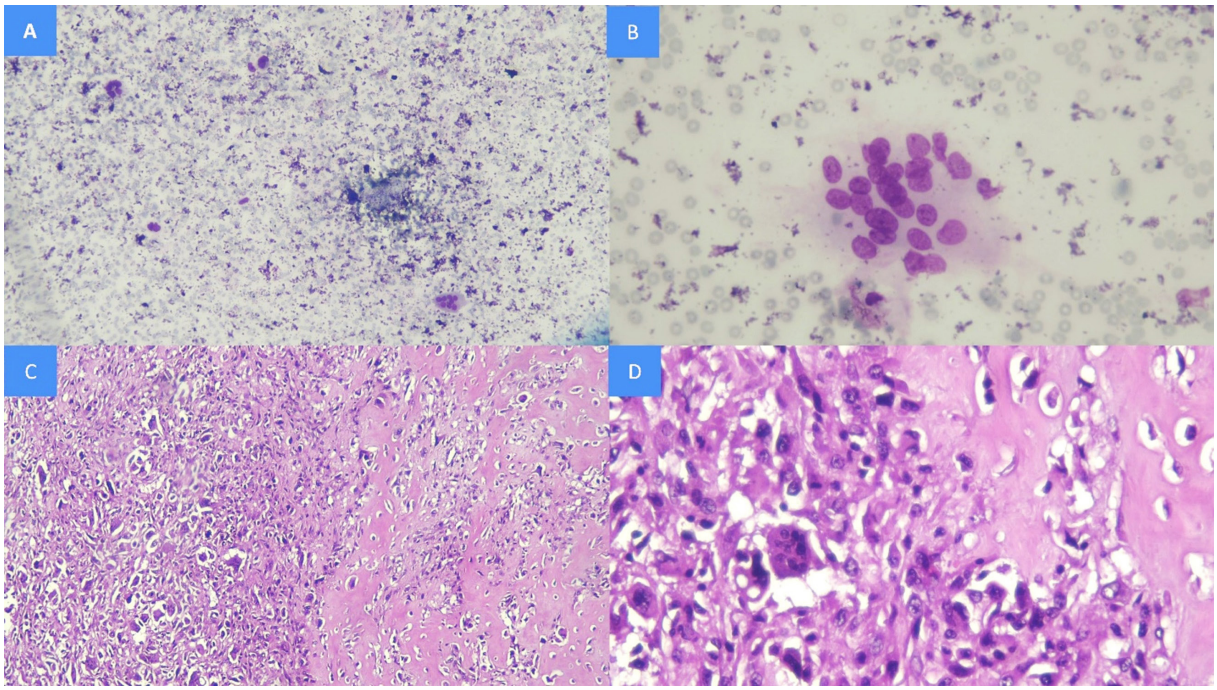

FIGURE 1. A) A representative image of FNAB showed multinucleated giant cells with necrotic debris as its background (Diff Quick,100x). B) On higher magnification, there is a multinucleated giant cell with 20-30 nuclei (Diff Quick, 400x). C) Confirmatory histopathology showed malignant tumor cells with high-grade polymorphic cells, nuclei ranging from round, oval, spindle, hyperchromatic with visible nucleoli, among them there are multinucleated giant cells (HE, 100x). D. On higher magnification, there are giant cells and surrounding tumor cells with osteoid matrix on the background (HE, 400x).

DISCUSSION

Fine needle aspiration biopsy is a minimally invasive, easy, and affordable method to diagnose musculoskeletal cases.[7] The accuracy of FNAB in various studies ranges from 75%-98%, where the accuracy was higher in the study with a larger sample size (>300 samples).[8-10] In this study, the accuracy of FNAB is 83%. This is already good, considering the sample used is below 100. Most of the false negative cases were caused by insufficient and acellular samples. This is possibly due to the problematic location of the lesion, the intact bone cortex, and the lesions that are cystic, necrotic, or hemorrhagic. In another study, it was stated that the percentage of insufficient samples reached 15%.[11] This, in turn, becomes the biggest challenge for FNAB in diagnosing musculoskeletal lesions. In this study, there were 5 cases of metastatic carcinoma from other organs, where the accuracy of FNA reaches 100% in metastatic patients. This is higher compared to other similar studies.[12-13]

Giant cell tumor was this study's most benign tumor finding. There are two false positive results of GCT with FNAB, whereas confirmatory histopathological showed a giant cell riched variant of osteosarcoma (FIGURE 1). Case one was a 59 y.o. patient with a tumor located at the distal radius. There is also one false positive case of 16 a 16 y.o. female with a tumor near the tibia. Fine needle aspiration biopsy result suggested an aneurysmal bone cyst. However, the histopathological result revealed conventional osteosarcoma, a giant cell-rich variant.

Diagnosis of GCT of the bone with FNA had many challenges compared with conventional biopsy since some bone tumors presented with multinucleated giant cell (osteoclast) or giant cell-like osteoclasts, such as GCT of the bone, GCT of Paget's disease, chondroblastoma, aneurysmal bone cyst, and giant cell riched subtype of osteosarcoma.[14] The ability to differentiate those entities is significant because it relates to prognosis and clinical management. The bone GCT has a preference in young adults and mainly affects the epiphysis of the long bones. At the same time, osteosarcoma mainly occurs on metaphysis-diaphysis of the long bones in adolescents and young adults, with predominance in male patients. The aneurysmal bone cyst usually occurs in the first two decades of life with a small predomination of females and mainly affects the metaphysis of the long bones.[15] On the nonspecific location or clinical presentation, mutation of H3G34W and immunohistochemistry (IHC) staining of H3K36M have high specificity to diagnose GCT of the bone and chondroblastoma. The negative result of H3F3A mutation and IHC of H3G34W lead to GCT of the bone diagnosis. Detection of H3F3A mutation with or without IHC staining of H3G34W could help differentiate between malignant GCT and osteosarcoma.[16] In the malignant tumor category, the most common diagnosis in this study was osteosarcoma. This finding was in line with a study by Jorda *et al.*[17] The updated management of osteosarcoma is chemotherapy before surgery, which showed the importance of FNAB as an early diagnostic method.[18]

There are ways to make FNAB more effective in diagnosing musculoskeletal lesions. One such way is by USG guidance, which helps in providing real-time visualization of the needle tip, making the procedure more reliable and secure.[19,20] However, there were some limitations in our study that need to be considered before interpreting the results. Firstly, we did not take into account whether the FNAB was done with an imaging guide or not. Secondly, some lesions had only one reported case, which may not be representative enough, and could affect the diagnostic study parameters.[17,21] Despite these limitations, this study showed that FNAB could be an effective early diagnostic tool for musculoskeletal lesions. These findings provide a basis for future research. However, to confirm the role of FNAB as a less invasive diagnostic technique in musculoskeletal cases, larger studies with adequate sample preparation, analysis of confounding variables, and a more comprehensive sample size are necessary.

CONCLUSION

Fine needle aspiration biopsy is a safe and effective early diagnostic method for detecting musculoskeletal lesions, including bone tumors, soft tissue sarcomas, and metastatic cancers. It is less invasive than other diagnostic methods, with minimal risks of complications, and provides accurate results. The obtained results help physicians to develop an appropriate treatment plan, leading to improved outcomes and quality of life for patients.

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Impact of multivessel coronary artery disease on early and late clinical outcome in ST-Segment elevation myocardial infarction patients who underwent percutaneous coronary intervention: insight from Indonesia

Arditya Damarkusuma*, Nahar Taufiq, Hendry Purnasidha Bagaswoto, Firandi Saputra, Daniel Sukmadja, Budi Yuli Setianto

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-RSUP Dr. Sardjito Yogyakarta Indonesia

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ABSTRACT

It is estimated that 15 people for every 1000 Indonesian residents suffer from cardiovascular disease (CVD) including ST-segment elevation myocardial infarction (STEMI). Percutaneous coronary intervention (PCI) is often performed in patients with STEMI. Several factors affect clinical outcome after PCI procedure including multivessel coronary artery disease. This study aimed to measure the impact of multivessel coronary artery disease on the early and late outcomes of STEMI patients undergoing PCI procedures. This was a prospective cohort study on STEMI patients undergoing PCI procedures from the period of August to December 2021. Two expected cohorts were performed i.e. patients who suffered from single-vessel disease (SVD) and patients who suffered from multivessel disease (MVD). Forty six patients with STEMI were enrolled in this study consisting of 24 (52.17%) patients with MVD and 22 (47.83%) patients with SVD. No significant difference in baseline characteristics between MVD and SVD groups was observed ($p > 0.05$). The MVD group (91.67%) used a more radial percutaneous approach compared with the SVD group (54.55%; $p = 0.04$). In addition, no significant difference between the SVD group and the MVD group in major adverse cardiovascular events (MACE) and echocardiographic outcome after 90-d follow up was observed ($p > 0.05$). In conclusion, MVD has similar impacts on early and late clinical outcomes compared with SVD in STEMI patients undergoing PCI procedures.

ABSTRAK

Diperkirakan 15 orang dari setiap 1000 penduduk Indonesia menderita penyakit kardiovaskular (CVD) termasuk infark miokard elevasi segmen ST (STEMI). Intervensi koroner perkutan (PCI) sering dilakukan pada pasien STEMI. Beberapa faktor mempengaruhi luaran klinis setelah prosedur PCI termasuk penyakit arteri koroner multivesel. Penelitian ini bertujuan untuk mengukur dampak penyakit arteri koroner multivesel terhadap luaran awal dan akhir pasien STEMI yang menjalani prosedur PCI. Penelitian ini merupakan studi kohort prospektif pada pasien STEMI yang menjalani prosedur PCI pada periode Agustus hingga Desember 2021. Dua kohort yang diharapkan dilakukan yaitu pasien yang menderita penyakit pembuluh darah tunggal (SVD) dan pasien yang menderita penyakit pembuluh darah ganda (MVD). Empat puluh enam pasien dengan STEMI dilibatkan dalam penelitian ini yang terdiri dari 24 (52,17%) pasien dengan MVD dan 22 (47,83%) pasien dengan SVD. Tidak ada perbedaan signifikan terhadap karakteristik awal antara kelompok MVD dan SVD yang diamati ($p > 0,05$). Kelompok MVD (91,67%) menggunakan pendekatan perkutan yang lebih radial dibandingkan dengan kelompok SVD (54,55%; $p = 0,04$). Selain itu, tidak ada perbedaan yang signifikan antara kelompok SVD dan kelompok MVD dalam hal kejadian efek samping kardiovaskular utama (MACE) dan hasil ekokardiografi setelah observasi 90 hari ($p > 0,05$). Kesimpulannya, MVD memiliki dampak serupa dalam hal luaran klinis awal dan akhir dibandingkan dengan SVD pada pasien STEMI yang menjalani prosedur PCI.

Keywords:
multivessel disease;
acute myocardial infarction;
percutaneous coronary intervention;
major adverse cardiovascular events

*corresponding author: arditya.dk@ugm.ac.id

INTRODUCTION

The burden of cardiovascular disease (CVD) remains the most prevalent killer disease in the world including in Indonesia.[1,2] It was estimated more than 17 million people died from cardiovascular disease worldwide. In Indonesia, it was reported that 15 people for every 1000 Indonesian residents suffer from cardiovascular disease.[2] Myocardial infarction (MI) is one of the life-threatening coronary-associated pathologies characterized by sudden cardiac death. Myocardial infarction accounts for one-third to one-half of the cases of CVD.

One-third of the MI manifested as ST-elevation myocardial infarction (STEMI) which urgently needed percutaneous coronary intervention (PCI).[3] Previous studies reported that a large number of STEMI patients were not able to undergo PCI due to limited facilities and human resources. Based on the guideline for STEMI management, the PCI procedure should be performed in less than 120 min to obtain optimal clinical outcome. However, only 25-60% of PCI procedures can achieve the ideal time as the guideline recommended. Therefore, 40-75% of STEMI patients had worse clinical outcomes after undergoing PCI procedure.[4-6]

The clinical outcome of the PCI procedure is affected by some factors including multiple vessel disease (MVD). However, studies of the effect of the MVD on clinical outcome of the PCI procedure are limited in Indonesia. This study was conducted to evaluate the impact of MVD on early and late clinical outcomes in STEMI patients undergoing the PCI procedure. This study will give benefits to patients, caregivers, and health policymakers.[7-9] Moreover, this study can also give insights to decide the preference of revascularization strategy in emergency PCI, between culprit vessel-only and complete vessel revascularization.

MATERIALS AND METHODS

Study design

This was a prospective cohort study with two expected cohorts. The first cohort was individual who suffered from single vessel disease (SVD). The second cohort was individuals who suffered from MVD.

Study population and subject

The study subjects were recruited consecutively from individuals who presented to the Emergency Department of Dr. Sardjito General Hospital, Yogyakarta with standard criteria of STEMI diagnosis. All patients who underwent primary PCI with a drug-eluting stent or bare metal stent implanted into the naïve coronary vessel within 24 h of onset were included. Exclusion criteria were applied when there was one of the conditions as follows: extensive coronary heart disease which was planned for coronary artery bypass graft procedure in 30-d, other non-cardiac disease comorbid which was life-threatening, and creatinine clearance <30 mL/min.

Coronary angiography procedure

The patient was prepped and draped after they arrived at the surgery laboratory. A local anesthesia was administered with 2% lidocaine. The sheath was inserted into the radial or femoral artery. A wire was inserted and subsequently catheter was advanced. Left and right coronary artery angiography were performed in multiple views (FIGURE 1).

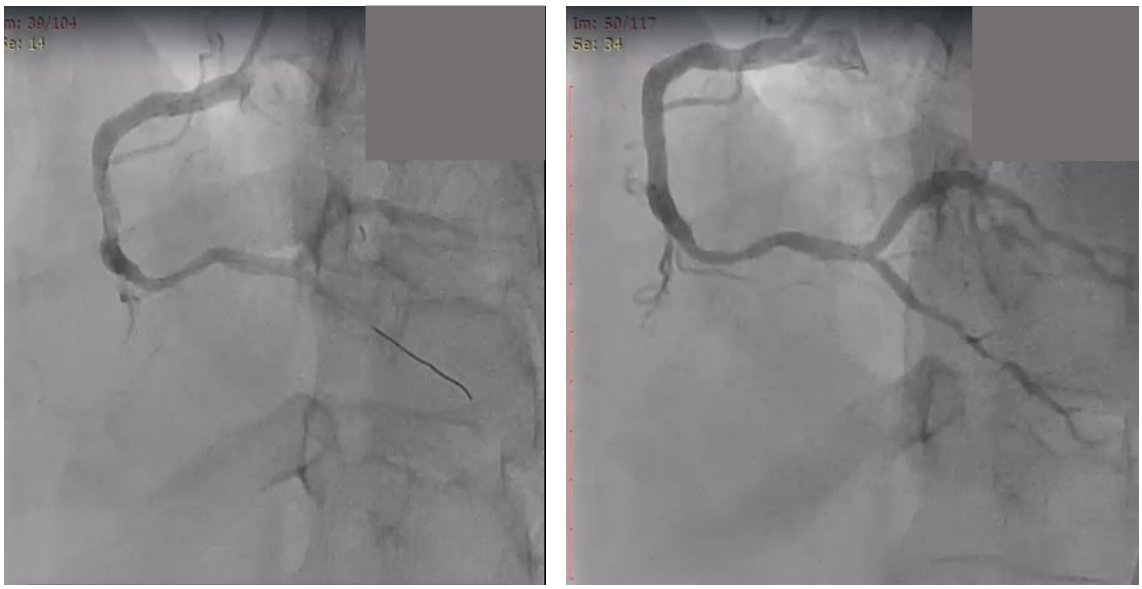

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FIGURE 1. Percutaneous coronary intervention procedure in Dr. Sardjito General Hospital. A) Before intervention in the right coronary artery; B) After intervention in the right coronary artery

RESULTS

The study included 46 patients, consist of 22 SVD and 24 MVD group, with mean ages of 54.55 ± 9.82 y.o. and 53.00 ± 9.94 y.o., respectively. No significant difference in baseline data characteristics were observed (TABLE 1). The radial percutaneous entry approach was more performed in MVD cases (91.67%) than in SVD cases (54.55%; p=0.04) (TABLE 2). In addition, the mean stent diameter in MVD cases (2.91 ± 0.29 mm) was smaller than in SVD cases (3.03 ± 0.31 mm; p = 0.04).

TABLE 1. Baseline characteristics of the subjects.

Baseline characteristics	SVD (n = 22)	MVD (n = 24)	p
Male [n (%)]	20 (90.91)	22 (91.67)	1.00
Age (mean ± SD yr)	54.55 ± 9.82	53.00 ± 9.94	0.60
GRACE score (mean ± SD)	101.35 ± 23.81	107.00 ± 22.02	0.42
Risk factors [n (%)]			
• Active smoker	17 (77.27)	21 (87.50)	0.10
• Past smoker	3 (13.63)	7 (29.17)	0.12
• Dyslipidemia	-	4 (16.6)	0.11
• Hypertension	14 (63.64)	17 (70.83)	0.60
• Diabetes mellitus	4 (18.18)	3 (12.50)	0.69
• Family history	-	1 (4.1)	1.00
• MI history	-	1 (4.1)	1.00
• Documented CAD	-	-	-
• History of heart failure	-	-	-

TABLE 1. Cont

Baseline characteristics	SVD (n = 22)	MVD (n = 24)	p
• History of CVD	1 (4.54)	1 (4.17)	1.00
• History PVD	-	-	-
• History of CKD	-	-	-
Mean admission HR (beats/min)	79.13 ± 17.61	80.38 ± 14.35	0.79
Mean admission SBP (mmHg)	135.95 ± 30.51	123.08 ±24.65	0.12
Mean admission DBP (mmHg)	81.59 ± 17.08	74.92 ± 12.66	0.37
Thrombolytics [n (%)]	5 (22.73%)	5 (20.83%)	1.00
Types of thrombolytics [n (%)]			
• Streptokinase	3 (13.63)	1 (4.17)	0.52
• Alteplase	2 (9.09)	4 (4.17)	0.52
Initial management [n (%)]			
• Heparin	15 (68.18)	22 (91.67)	0.06
• Aspirin	22 (100.00)	24 (100.00)	-
• Clopidogrel 75 mg	1 (4.54)	-	0.48
• Clopidogrel 300 mg	1 (4.54)	6 (25.00)	0.10
• Clopidogrel 600 mg	20 (90.91)	18 (75.00)	0.41
Laboratory result (mean ± SD)			
• Creatinine (mg/dL)	1.08 ± 0.20	1.18 ± 0.56	0.43
• Hb (g/dL)	14.75 ± 1.58	14.08 ± 1.65	0.16
• Hct (%)	42.80 ± 4.53	41.59 ± 4.52	0.37
• Leukocyte (x 10^3/µL)	13.71 ± 4.34	13.31 ± 2.77	0.71
• Thrombocyte (x 10^3/µL)	289.72 ± 99.74	289.96 ± 127.40	1.00
• Neutrophil (%)	77.64 ± 8.23	79.40 ± 7.34	0.45
• Lymphocyte (%)	14.74 ± 7.84	13.33 ± 6.68	0.52
• Monocyte (%)	6.01 ± 2.32	6.06 ± 1.87	0.93
• Eosinophil (%)	0.69 ± 0.73	0.58 ± 0.81	0.64
• Basophil (%)	0.88 ± 3.33	0.15 ± 0.13	0.28
• Hs-troponin on admission (g/dL)	23644.25 ± 18724.10	16732.63 ± 6461.00	0.22
• Hs-troponin on discharge (g/dL)	25680.40 ± 13535.08	26643.95 ± 14120.50	0.82
• Fasting blood glucose (mg/dL)	136.81 ± 38.96	137.96 ± 50.69	0.93
• HbA1C (%)	6.73 ± 1.42	6.70 ± 1.93	0.98
• Total cholesterol (mg/dL)	189.29 ± 41.87	189.04 ± 40.35	0.98
• LDL (mg/dL)	125.41 ± 34.08	126.08 ± 42.01	0.95
BMI (mean ± SD kg/m^2)	24.51 ± 3.36	24.60 ± 3.38	0.93
ECG on admission			
• Sinus	18 (81.82)	20 (83.33)	1.00
• Junctional	-	1 (4.17%)	1.00
• Atrial fibrillation	-	-	-
• AV block	4 (18.18)	3 (12.50)	0.69
Region of STEMI			
• Anterior	14 (63.64)	16 (66.67)	0.83
• Lateral	7 (18.18)	2 (8.33)	0.07

TABLE 1. Cont

Baseline characteristics	SVD (n = 22)	MVD (n = 24)	p
• Inferior	8 (31.82)	9 (37.50)	0.94
• Posterior	4 (18.18)	5 (20.83)	1.00
• Righr sided	6 (27.27)	5 (20.83)	0.61
Killip [n (%)]			
• I	21 (95.45)	20 (83.33)	0.35
• II	1 (4.54)	3 (12.50)	0.63
• III	-	-	-
• IV	-	1 (4.17)	1.00
Ischemic time (mean ± SD hr)	13.50 ± 9.96	23.65 ± 23.25	0.11
Wire crossing time (mean ± SD min)	179.44 ± 88.93	177.95 ± 157.112	0.97
Length of stay (mean ± SD d)	5.23 ± 1.82	4.63 ± 1.31	0.20

Note: SVD= single vessel disease; MVD=multiple vessel disease; GRACE=global registry of acute coronary events; MI=myocardial infarction; STEMI=ST-elevation myocardial infarction; CAD= cardiac artery disease; CVD= cardiovascular disease; PVD= peripheral vascular disease; CKD= choric kidney disease; HR= heart rate; SBP= systolic blood pressure; DBP= diastolic blood pressure; BMI= body mass index; ECG= electrocardiogram.

TABLE 2. PCI procedure characteristics of the subjects.

PCI procedure characteristics	SVD (n = 22)	MVD (n = 24)	p
Radial percutaneus entry [n (%)]	12 (54.55)	22 (91.67)	0.04
Culprit lesion [n (%)]			
• LAD	13 (59.09)	14 (58.33)	0.98
• LCX	-	-	-
• RCA	8 (36.36)	9 (37.50)	0.69
• Left main	1 (4.55)	1 (4.17)	1.00
Fluoroscopy time (mean ± SD min)	30.86 ± 45.13	22.58 ± 14.50	0.40
Contrast volume (mL)	144.50 ± 44.54	164.58 ± 70.77	0.28
Total dose (mGy)	850.64 ± 704.36	1325.38 ± 1740.387	0.24
PCI status [n (%)]			
• Primary PCI	19 (86.36)	19 (79.17)	0.70
• Rescue PCI	1 (4.54)	2 (8.33)	1.00
• Pharmacoinvasive PCI	2 (9.09)	3 (12.50)	1.00
Coronary dominance [n (%)]			
• Right	22 (100.00)	23 (95.83)	1.00
• Left	-	-	-
• Co dominance	-	1 (4.17)	1.00
Lesion [n (%)]			
• Ostial	-	-	-
• LMS	-	-	-
• CTO	1 (4.54)	3 (11.11)	0.48
• Thrombus	18 (81.82)	21 (11.78)	0.69

TABLE 2. Cont

PCI procedure characteristics	SVD (n = 22)	MVD (n = 24)	p
• Calcified	2 (9.09)	3 (11.11)	0.60
Pre PCI TIMI flow [n (%)]			
• 0	10 (45.45)	13 (43.33)	0.86
• 1	1 (4.54)	-	1.00
• 2	4 (18.18)	7 (23.33)	0.73
• 3	7 (31.82)	10 (33.33)	0.90
Post PCI TIMI flow [n (%)]			
• 0	-	1 (3.44)	1.00
• 1	-	-	-
• 2	1 (4.54)	4 (13.79)	0.61
• 3	21 (95.45)	24 (82.76)	0.61
Guide catheter French size [n (%)]			
• 6	20 (90.91)	21 (87.50)	1.00
• 7	2 (9.09)	3 (12.50)	1.00
Dissection post procedure [n (%)]	-	1 (4.17)	1.00
Slow or no reflow [n (%)]	1 (4.54%)	5 (20.83)	0.24
Number of stent per lesion treated			
• 1	17 (77.27)	15 (83.33)	0.10
• 2	4 (18.18)	8 (33.33)	0.24
• 3	1 (4.54)	3 (12.50)	0.61
Stent diameter (mean ± SD mm)	3.03±0.31	2.91±0.29	0.04
Stent length (mean ± SD mm)	30.50±31.00	29.56±7.05	0.83
Intracoronary device [n (%)]			
• Aspiration catheter	1 (4.54)	-	1.00
• Microcatheter	-	1 (4.17)	1.00
• Extension catheter	-	-	-
• POBA	1 (4.54)	-	1.00

Note: SVD=single vessel disease; MVD=multiple vessel disease; PCI= percutaneous coronary intervention; LAD= left anterior descending artery; LCX= left circumflex artery; RCA= right coronary artery; LMS=left main stem; CTO=chronic total occlusion; TIMI= thrombolysis in myocardial infarction; POBA=percutaneous old balloon angioplasty

No significant difference between SVD cases and MVD cases groups in the parameters of ejection fraction (EF), left ventricular internal diameter end diastole (LVIDd), left atrial volume index (LAVI), tricuspid annular plane systolic excursion (TAPSE), global longitudinal strain (GLS), ΔEF, ΔTAPSE, ΔGLS ($p > 0.05$) after 30-d and 90-d of follow up was observed (TABLE 3-5).

On 90-d of observation in the SVD cases group, one patient suffered from an ischemic stroke on the 28th day after PCI. In the MVD cases group, one patient with cardiovascular was died on the 7th day and reinfarction occurred in one patient on the 62nd day (TABLE 6).

TABLE 3. 12-h post PCI echocardiographic profile.

Echocardiographic profile	SVD	MVD	p
LAVI (mean ± SD mL/m^2)	22.75 ± 3.72	20.33 ± 3.51	0.64
LVIDd (mean ± SD mm)	49.00 ± 2.80	53.00 ± 2.74	0.21
EF (mean ± SD %)	46.55 ± 9.16	45.13 ± 9.49	0.72
TAPSE (mean ± SD mm)	17.75 ± 2.50	20.33 ± 2.32	0.24

Note: SVD=single vessel disease; MVD=multiple vessel disease; LAVI= left atrial volume index; LVIDd= left ventricular internal diameter end diastole; EF= ejection fraction.

TABLE 4. 30-d echocardiographic profile.

Echocardiographic profile	SVD	MVD	p
LAVI (mean ± SD mL/m^2)	27.50 ± 9.15	30.69 ± 9.09	0.45
LVIDd (mean ± SD mm)	50.75 ± 5.50	53.85 ± 6.47	0.28
EF (mean ± SD %)	45.38 ± 12.35	46.53 ± 16.05	0.86
TAPSE (mean ± SD mm)	20.02 ± 4.03	19.46 ± 2.70	0.72
GLS (mean ± SD %)	-11.48 ± 6.18	-10.04 ± 9.08	0.95
ΔEF (mean ± SD %)*	3.25 ± 15.95	2.85 ± 12.97	0.95
ΔTAPSE (mean ± SD mm)**	2.63 ± 4.60	1.85 ± 2.76	0.63

Note: MVD=multivessel disease; SVD=single vessel disease; LAVI= left atrial volume index; LVIDd= left ventricular internal diameter end diastole; EF= ejection fraction; TAPSE= tricuspid annular plane systolic excursion; GLS= global longitudinal strain; *ΔEF= ejection fraction mean difference between 12-h and 30-d of follow up; **ΔTAPSE= tricuspid annular plane systolic excursion mean difference between 12-h and 30-d of follow up

TABLE 5. 90-d echocardiographic profile.

Echocardiographic profile	SVD	MVD	p
LAVI (mL/m^2)	25.63 ± 9.04	24.25 ± 4.40	0.70
LVIDd (mm)	51.72 ± 5.73	48.38 ± 3.42	0.16
EF (%)	45.45 ± 14.79	56.13 ± 17.12	0.16
TAPSE (mm)	18.64 ± 4.48	21.75 ± 2.38	0.09
GLS (%)	-12.60 ± 5.65	-15.51 ± 4.96	0.27
ΔEF (%)*	-1.27 ± 20.77	8.38 ± 18.79	0.31
ΔTAPSE (mm)**	-1.45 ± 6.95	3.02 ± 3.07	0.11
ΔGLS (%)***	-0.69 ± 1.95	-5.48 ± 9.51	0.30

Note: MVD=multivessel disease; SVD=single vessel disease; LAVI= left atrial volume index; LVIDd= left ventricular internal diameter end diastole; EF= ejection fraction; TAPSE= tricuspid annular plane systolic excursion; GLS= global longitudinal strain; *ΔEF= ejection fraction mean difference between 12-h and 90-d of follow up; **ΔTAPSE= tricuspid annular plane systolic excursion mean difference between 12-h and 90-d of follow up; ***ΔGLS= global longitudinal strain mean difference between 30-d and 90-d of follow up

TABLE 6. Major adverse cardiovascular events in 90-d of observation

Echocardiographic profile	SVD	MVD	Observation day	p
Cardiovascular death	-	1	7	1.00
Reinfarction	-	1	62	1.00
Target vessel revascularization	-	-	-	-
Stroke	1	-	28	0.64
Total	1	2		1.00

Note: MVD=multivessel disease; SVD=single vessel disease

DISCUSSION

Similarities in the baseline demographic profile, atherosclerotic risk factors, initial evaluation, laboratory examination profile, Killip categorization, ischemia, and wire crossing time were reported in this study. From the descriptive data, it could be concluded that the wire crossing time from MVD disease (179.44 ± 88.93 min) and SVD case groups (177.95 ± 157.11 min) still could not achieve the ideal target of 120 min. More delay in wire crossing time was related to a higher risk of cardiovascular adverse events to occur.[10]

Most of the general characteristics in the PCI procedure data (type of PCI strategy, culprit vessel, lesion type, TIMI flow, intracoronary device, and periprocedural complication) were similar between the two groups ($p > 0.05$). In the MVD case group (91.67%), it was reported that the radial percutaneous entry approach was more often performed compared with the SVD case group (54.55%; $p = 0.04$). Previous studies reported that the radial approach provided a more beneficial outcome compared with the femoral approach. This radial approach would reduce the number of periprocedural adverse events, morbidity, and mortality.[11,12] However in this study, no significant differences of clinical outcomes between radial and femoral access ($p>0.05$). It was also reported that the stent diameter used in the MVD case group (2.91 ± 0.29 mm) was smaller compared with the SVD case group (3.03 ± 0.31 mm; $p = 0.04$). Plitt *et al.*[10] reported that in population of acute myocardial infarction and stable coronary artery disease patients, smaller stent diameter contributes to higher risk of major adverse cardiovascular events, driven by the increased rate of repeat revascularization.

One reinfarction event and one cardiovascular death were the two main adverse cardiovascular events discovered over the 90-day outcome follow-up period in the MVD case group. Furthermore, in the SVD case group, major adverse cardiovascular event or stroke was observed in one patient. No significant difference in major adverse cardiovascular events after 90-d follow up was observed. Anello *et al.*[13] also reported that there is no significant difference in major adverse cardiovascular events among Brazilian patients with single vessel and multiple vessel coronary artery disease younger than 50 y.o. undergoing coronary stent implantation. Furthermore, it was concluded from that the MVD has similarity in major adverse cardiovascular events compared with the SVD after underwent PCI procedure.[13]

In this study, the echocardiographic results including EF, TAPSE, LVIDd, LAVI, GLS, ΔEF, ΔTAPSE, and ΔGLS were not significantly different between the MVD case group compared with the SVD case group after 30-d and 90-d follow-up (TABLE 5). Although the MVD case group

had higher in EF and TAPSE as well as lower in LVIDd and LAVI, however they were not significantly different (p>0.05). The insignificant outcome difference in this study could be caused by some limitations of this study, including small sample size, short duration of follow-up, and difference in angiographic characteristics.

CONCLUSION

In conclusion, MVD has similar impacts on early and late clinical outcomes compared with SVD in STEMI patients undergoing PCI procedures. Revascularization of culprit vessel-only can be more considered than a complete revascularization strategy. However, further study with a larger sample size and longer duration of outcome follow-up is needed.

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Association between CDK4 expression and overall survival of osteosarcoma patients

Faizah Dwi Tirtasari[1], Fikar Arsyad Hakim[1], Yudha Mathan Sakti[2], Sumadi Lukman Anwar[3], Rheza Gandi Bawono[1], Ery Kus Dwianingsih[1]*

[1]Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, [2]Department of Surgery, Orthopedics and Traumatology Division, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/ Sardjito General Hospital, Yogyakarta, Indonesia, [3]Department of Surgery, Oncology Division, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/ Sardjito General Hospital, Yogyakarta, Indonesia.

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ABSTRACT

Osteosarcoma is the most common primary bone tumor malignancy, accounting for 30 - 80% of all primary bone tumors. It is presented in a bimodal distribution manner with the age of onset divided into two groups, 10-20 and >60 y.o. Various factors have significance in the patient's prognosis, including the expression of cyclin-dependent kinase 4 (CDK4). This CDK4 has an essential role in the pathogenesis of osteosarcoma through inactivation of the Rb gene, which is associated with the patient's survival. This study was conducted to evaluate the correlation between CDK4 expression and the survival of osteosarcoma patients. It was a cross-sectional study involving 50 patients diagnosed with osteosarcoma based on clinical, radiological, and histopathological examination. Available formalin-fixed paraffin-embedded (FFPE) samples were retrieved for immunohistochemical (IHC) staining of CDK4. The survival data was collected from medical records. CDK4 expression and survival data were analyzed statistically using the Kaplan-Meier curve. Out of 50 subjects, CDK4 was found to be expressed in 38 samples (76%). The group with negative CDK4 showed a slightly longer overall survival (by 0.2 mo) than the positive CDK4 group. However, these results were not statistically significant (p = 0.821). In conclusion, the overexpression of CDK4 may not directly affect the survival rate in osteosarcoma. Other factors need to be considered to understand the complexity of the disease.

ABSTRAK

Osteosarkoma merupakan keganasan tumor tulang primer yang paling umum terjadi, mencakup 30 - 80% dari seluruh tumor tulang primer. Pola distribusi osteosarcoma berbentuk bimodal dengan onset umur dibagi menjadi dua kelompok, yaitu 10-20 dan >60 tahun. Berbagai faktor berperan penting dalam prognosis pasien, termasuk ekspresi dari *cyclin-dependent kinase* 4 (CDK4). CDK4 memiliki peran penting dalam patogenesis osteosarkoma melalui inaktivasi gen Rb, yang berhubungan dengan survival pasien. Penelitian ini dilakukan untuk mengkaji hubungan antara ekspresi CDK4 dan survival pada pasien osteosarkoma. Penelitian ini merupakan penelitian potong lintang yang melibatkan 50 pasien yang didiagnosis osteosarkoma berdasarkan pemeriksaan klinis, radiologi, dan histopatologi. Sampel *formalin-fixed paraffin-embedded* (FFPE) yang tersedia diambil untuk pewarnaan imunohistokimia (IHC) CDK4. Data survival dikumpulkan dari rekam medis. Ekspresi CDK4 dan data survival dianalisis secara statistik menggunakan kurva Kaplan-Meier. Dari 50 subjek penelitian, ekspresi CDK4 didapatkan pada 38 (76%) sampel. Keseluruhan survival pada kelompok CDK4 negatif adalah 0,2 bulan lebih lama dibandingkan kelompok CDK4 positif; namun tidak menunjukkan perbedaan yang bermakna secara statistik (p = 0,821). Simpulan, ekspresi CDK4 yang berlebihan tidak secara langsung mempengaruhi tingkat kelangsungan hidup pada osteosarkoma. Faktor-faktor lain perlu dipertimbangkan untuk memahami kompleksitas penyakit ini.

Keywords:
CDK4 expression;
osteosarcoma;
survival;
bone cancer;
prognosis

*corresponding author: ery_malueka@ugm.ac.id

INTRODUCTION

Osteosarcoma is the most common type of primary bone cancer. It accounts for 30 - 80% of all primary bone tumors.[1] The incidence rate is 5.6 cases per 1,000,000 people annually.[2] Between the ages of 15 and 19, the number of cases of osteosarcoma has increased to an estimated 8 - 11 per 1,000,000 people annually. Data from Dr. Cipto Mangunkusumo Hospital, Jakarta demonstrated that a total of 219 cases of osteosarcoma were recorded between 1995 and 2007, averaging 16.8 cases annually. Osteosarcoma was responsible for 70.59% of all bone malignancies, making it the most common type. The highest number of cases occurred during the second decade of life.[3] Osteosarcoma is a type of cancer that mostly affects the bones of the body. It is more common in men than women, with a ratio of 3:2. This is because men have a longer period of bone growth than women. The most common age range for osteosarcoma is between 10 and 25 yr. However, it can also occur in people who are 60 y.o. or older, which is why it is known as a cancer with bimodal distribution.[4] Before the advent of effective chemotherapy, the overall 2-yr survival rate for patients with osteosarcoma was between 15% and 20% after undergoing surgical resection and radiotherapy.[5]

Uncontrolled cell proliferation and growth are key characteristics of cancer. Cyclin-dependent kinases (CDKs) play a vital role in regulating the cell cycle. However, due to genetic and epigenetic changes that affect their regulatory pathways, CDKs are often overexpressed or overactive in tumors. This leads to a loss of checkpoint integrity, resulting in uncontrolled cell growth and malignant transformation.[6,7] Among CDKs, cyclin-dependent kinase-4 (CDK4) is a type of kinase that plays a crucial role in regulating the G1-S phase of the cell cycle. It does this by deactivating a tumor suppressor protein called retinoblastoma (Rb) in both cancer cells and during cell division. When stimulated to proliferate, CDK4 combines with cyclin D1 to induce the phosphorylation of Rb (pRb) and weaken its gene suppressor function. This leads to pRb no longer being able to bind to the transcription factor E2F, which in turn promotes the transcription of multiple cell cycle and anti-apoptotic genes, ultimately causing cancer cells to grow.[8]

In osteosarcoma, Rb and p53 gene abnormalities were commonly observed. The Rb protein family, has three distict binding domains and interacts with the E2F transcription factor family, a regulatory protein. The E2F transcription family consists of six members, with each E2F member having a DNA binding and dimerization domain. E2F-1 to E2F-5, which stimulate transcription, binds to various Rb protein families, including pRb, pRb2/p130, and p107, and is regulated by the cell cycle. E2F-1, E2F-2, and E2F-3 bind to pRb, while E2F-4 and E2F-5 bind to p107 or p130. By adolescence, 70% of all osteosarcomas contain Rb mutations. Alteration in mesenchymal progenitor cells and initiation of osteosarcoma due to loss of Rb and p53 have been demonstrated *in vivo*.[8]

Cyclin-dependent kinase-4 has recently been identified as a potential therapeutic target in several types of cancer, including human breast cancer, liposarcoma, glioblastoma, and melanoma. Due to its significance in cancer cells, CDK4 inhibitors become one of the promising candidates for the treatment of various cancers.[9] Several investigators conducted immunohistochemical studies using a human osteosarcoma tissue microarray to evaluate CDK4 expression and their correlation with pathological characteristics and clinical significance in patients with osteosarcoma. Immunohistochemistry staining revealed that the nucleus of

osteosarcoma cells was immunoreactive with CDK4, consistent with in vitro study where CDK4 expressed predominantly in the nucleus of osteosarcoma cells using immunofluorescence tests.[7]

This study aimed to investigate an association between the expression of CDK4 and the survival of patients with osteosarcoma. Several findings suggest that CDK4 plays a crucial role in suppressing tumor suppressor gene function, and it may determine the survival of patients with malignancies.

MATERIAL AND METHODS

Samples and data collection

This cross-sectional study was conducted at the Department of Anatomical Pathology of Dr. Sardjito General Hospital in Yogyakarta, from January 1, 2012, to June 30, 2020. The study involved patients who were clinically, radiologically, and pathologically diagnosed with osteosarcoma. Fifty eligible patients' formalin-fixed paraffin-embedded (FFPE) samples were collected for the study. Two pathologists reviewed and reclassified all pathological specimens according to the WHO Classification of Tumors of Soft Tissue and Bone. The research protocol has been reviewed and approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital (KE/FK/1393/EC/2019).

Immunochemistry staining

Samples of FFPE were tested for osteocalcin (R&D; Biocare Medical, USA) to confirm the diagnosis of osteosarcoma. Subsequently, the samples were sliced into 3µm thickness for CDK4 immunostaining examination. Sections of FFPE were incubated, deparaffinized, and rehydrated. Antigen retrieval was conducted with the use of a decloaking chamber (Biocare Medical, USA). The mouse monoclonal antibody against CDK4 (Biocare Medical, USA) was used by diluting in phosphate buffer saline by a 1:100. Diamino-benzidine was applied to visualize the positive cells.

Interpretation of CDK4 immunostaining results

An independent pathologist evaluated CDK4-positive cells in a high-power field under a light microscope to assess CDK4 expression using the average method. The assessment was performed by two independent pathologists. The evaluation of CDK4 expression was adapted from Zhou *et al.*[7] by dividing the result into six groups: 0, no stained found in the tumor cell nucleus; 1+: positively stained in <10% of tumor cell nucleus; 2+: positively stained in 10% -25% of the tumor cell nucleus; 3+: positively stained in 26% -50% of the tumor cell nucleus; 4+: positively stained in 51% -75% of the tumor cell nucleus; 5+: positively stained in > 75% of the tumor cell nucleus. Tumors with a staining score of ≥3 were categorized into groups with overexpressed CDK4, and ≤2 were classified with underexpressed CDK4.

Statistical analysis

The association of CDK4 with overall survival was analyzed using the Kaplan-Meier curve. A p-value < 0.05 was considered statistically significant.

RESULTS

The demographic and clinicopathological features of the research subjects are summarized in TABLE 1. Two observers' data from the measurement of CDK4 were tested for Cohen's Kappa reliability to determine the consistency of measurements. The results showed good consistency with

a value of 0.673, which falls within the range of 0.61-0.80. The study consisted of 50 patients whose average age was 25.44 y.o. Out of these patients, 31 (62%) were younger than 25 y.o., 16 (32%) were aged between 25-59 y.o., and three patients (6%) were over 59 y.o. The study also included 32 male patients (64%) and 18 female patients (36%). Furthermore, 39 patients (78%) had primary tumors in their extremities, while 11 patients (22%) had primary tumors not located in the extremities area (TABLE 1). Out of the 50 samples assessed for histological grading, 46 of them (92%) were classified as high-grade osteosarcomas, while only 4 samples (8%) were classified as low-grade osteosarcomas. The majority of the osteosarcoma types were conventional osteosarcomas, which included osteoblastic and chondroblastic subtypes (FIGURE 1). Each subtype accounted for 13 samples, which is 26% of the total samples assessed. Based on the radiological examination, 23 out of 50 samples (46%) showed metastases, while the remaining 27 samples (54%) showed no evidence of metastasis. At the time of sample collection, 32 patients (64%) had already passed away, while the remaining 18 patients (36%) were still alive as of June 2020 (TABLE 1).

TABLE 1. Demographic and clinicopathological features of the subjects

Characteristics	n (%)
Sex	
• Male	32 (64.0)
• Female	18 (36.0)
Age group (yr)	
• < 25	31 (62.0)
• 25-59	16 (32.0)
• ≥ 60	3 (6.0)
Subtype	
• Osteoblastic	13 (26.0)
• Fibroblastic	4 (8.0)
• Chondrobalstic	13 (26.0)
• Giant cell rich	5 (10.0)
• Epithelioid	2 (4.0)
• Teleangiectatic	3 (6.0)
• Fibroblastic with chondroblastic parts	1 (2.0)
• Giant cell rich with fibroblastic parts	1 (2.0)
• Giant cell rich with chondroblastic parts	1 (2.0)
• Extraskeletal	3 (6.0)
• Parosteal	2 (4.0)
• Periosteal	1 (2.0)
• Low-grade intraosseous (central)	1 (2.0)

TABLE 1. Demographic and clinicopathological features of the subjects (cont.)

Characteristics	n (%)
Metastasis	
• Without metastasis	27 (54.0)
• Metastasis	23 (46.0)
Location	
• Extremity	39 (78.0)
• Non-extremity	11 (22.0)
Histologic grading	
• Low grade	4 (8.0)
• High grade	46 (92.0)
Pathologic staging	
• Unstaging	20 (40.0)
• Staging	30 (60.0)
T (Size)	
• Tx	0 (0.0)
• T0	0 (0.0)
• T1	5 (10.0)
• T2	25 (50.0)
• T3	0 (0.0)
N (Lymph nodes)	
• Nx	23 (46.0)
• N0	6 (12.0)
• N1	1 (2.0)
M (Metastasis)	
• Mx	29 (58.0)
• M0	0 (0.0)
• M1a	0 (0.0)
• M1b	1 (2.0)
Status	
• Alive	32 (64.0)
• Died	18 (36.0)

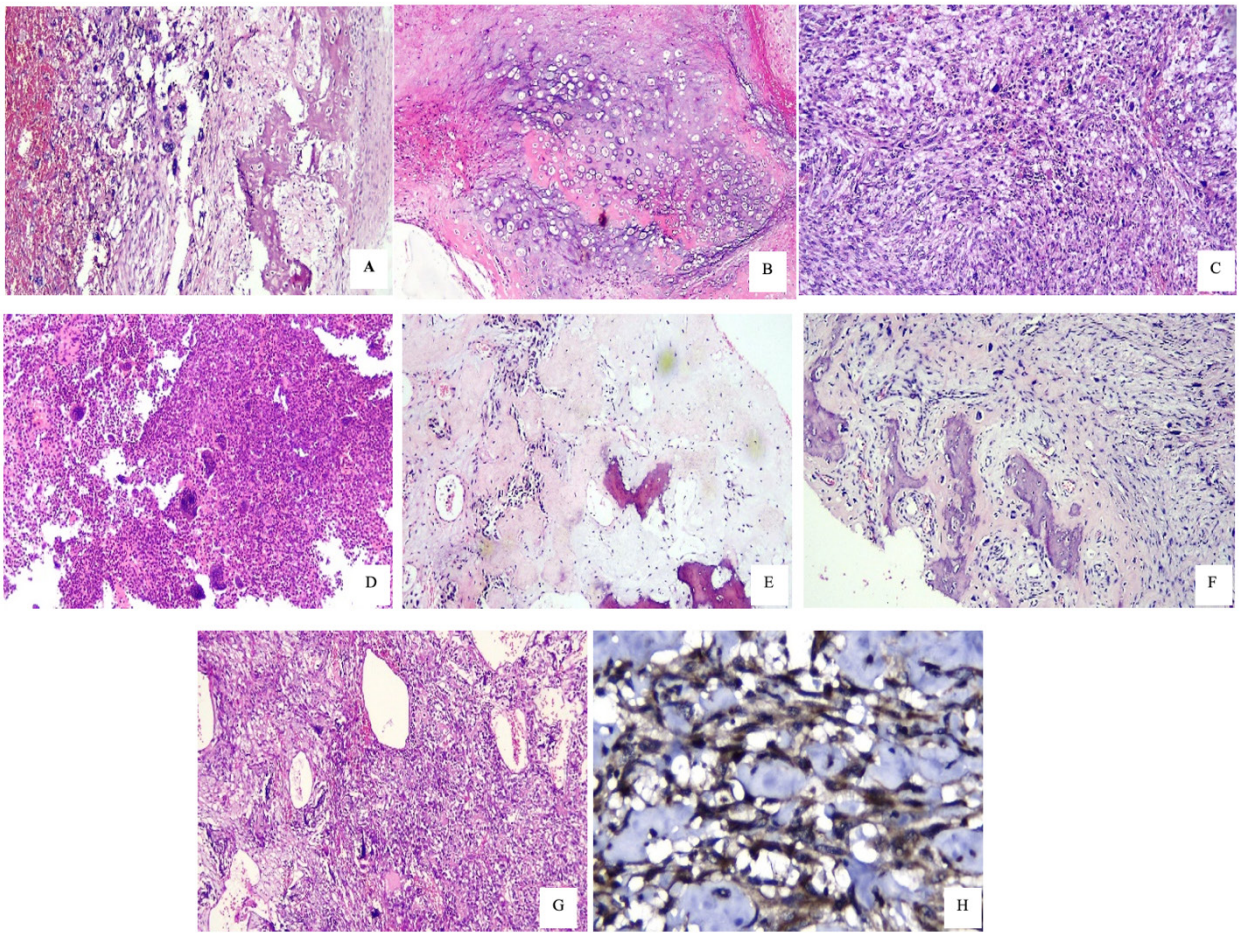

FIGURE 1. Representative images of osteosarcoma subtype. Osteoblastic osteosarcoma (HE 100x); B. Chondroblastic osteosarcoma (HE 100x); C. Fibroblastic osteosarcoma (HE 100x); D. Giant cell-rich osteosarcoma (HE 100x); E. Periosteal osteosarcoma (HE 100x); F. Parosteal osteosarcoma (HE 100x); G. Telangiectatic osteosarcoma (HE 100x); H. Immunohistochemical staining of osteocalcin expressed in the cytoplasm of tumor cells (original magnification 400×).

No significant relationship in CDK4 expression with all external variable was observed in this study (TABLE 2) including sex (p = 1.000), histological grading (p = 1.000), metastasis (p = 0.750), age (p = 0.729), pathological staging (p = 0.427), tumor location (p = 0.424), and mortality status (p = 0.309).

A study for up to 90 mo from 50 osteosarcoma patients with complete clinical information to investigate the association between CDK4 expression and overall survival in osteosarcoma patients was conducted. Of 50 samples, 38 (76%) expressed CDK4, while 12 (24%) did not. Among those expressing CDK4, low expression was found in 20 samples (52.6%), and high expression of CDK4 was found in 18 samples (47.4%) (FIGURE 2).

The survival of from 6 mo to 3 yr were presented in FIGURE 3. Overall survival in the patients with negative CDK4 stain was 23.6 mo, while the patients with positive CDK4 stain was 23.4 mon (TABLE 3). Overall survival in the negative CDK4 group was 0.2 mo longer than in the positive CDK4 group (FIGURE 4). However, it did not show a significant difference (p = 0.821) (TABLE 3). This study also found that CDK4 was not a significant predictor of mortality (p = 0.823) (TABLE 4).

TABLE 2. Characteristics of study subjects with CDK4 expression

Characteristics	CKD4 expression		p
	Negative	Positive	
Total subjects	12 (24.0)	38 (76.0)	
Sex			
• Male	8 (66.7)	24 (63.2)	1.000**
• Female	4 (33.3)	14 (36.8)	
Age group			
• < 25	7 (58.3)	24 (63.2)	
• 25-59	4 (33.3)	12 (31.6)	0.729***
• ≥ 60	1 (8.3)	2 (5.3)	
Metastasis			
• Without metastasis	6 (50.0)	21 (55.3)	0.750*
• Metastasis	6 (50.0)	17 (44.7)	
Location			
• Extremity	8 (66.7)	31 (81.6)	0.424**
• Non-extremity	4 (33.30	7 (18.4)	
Histologic Grading			
• Low grade	1 (8.3)	3 (7.9)	1.000**
• High grade	11 (91.7)	35 (92.1)	
Pathologic staging			
• Localized	7 (100)	21 (91.3)	
• Regional	0 (0.0)	1 (4.3)	0.427***
• Distant	0 (0.0)	1 (4.3)	
Status			
• Alive	6 (50.0)	26 (68.4)	0.309**
• Died	6 (50.0)	12 (31.6)	

*:Chi-square; **:Fisher exact test; ***:Mann Whitney

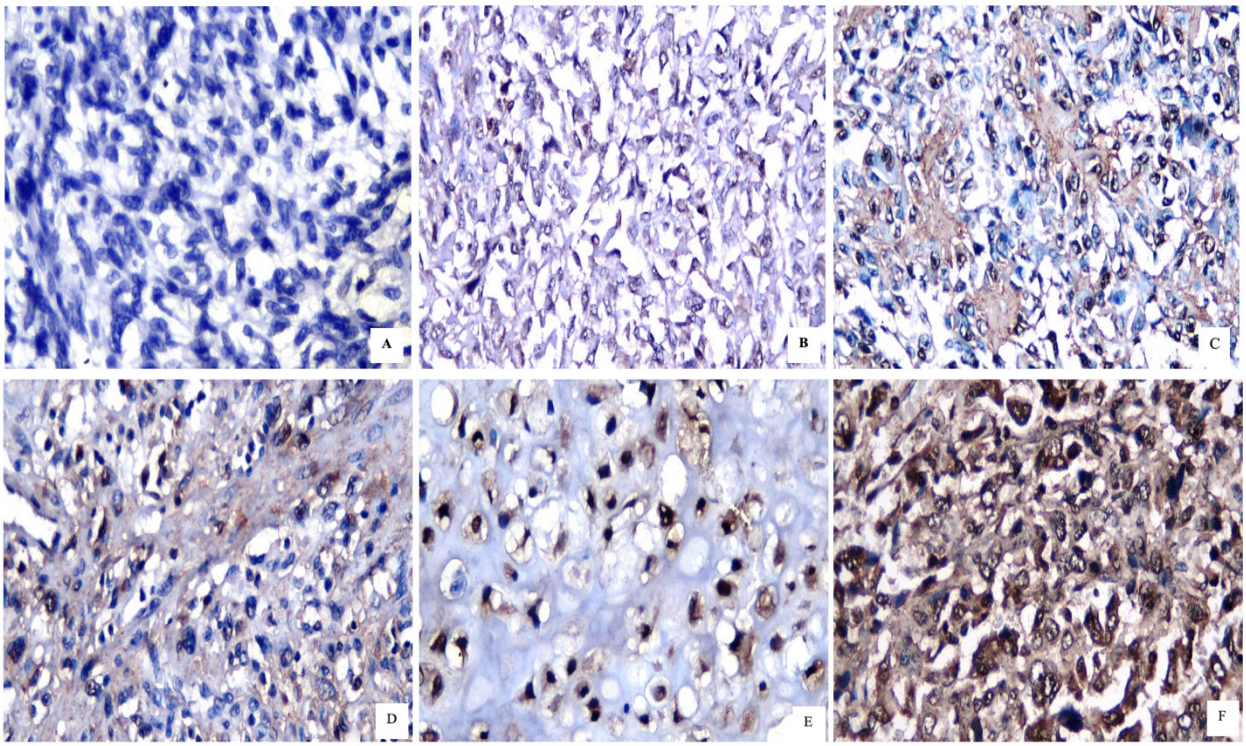

FIGURE 2. Representative images of different immunohistochemical staining intensities of CDK4. Based on the percentage of cells with positive nuclear staining, CDK4 staining patterns were categorized into six groups: 0, no nuclear staining (A); 1+: <10% of positive cells (B); 2+, 10%-25% of positive cells (C); 3+, 26%-50% of positive cells (D); 4+, 51%-75% of positive cells (E); and 5+, >75% of positive cells (F). Original magnification 400×.

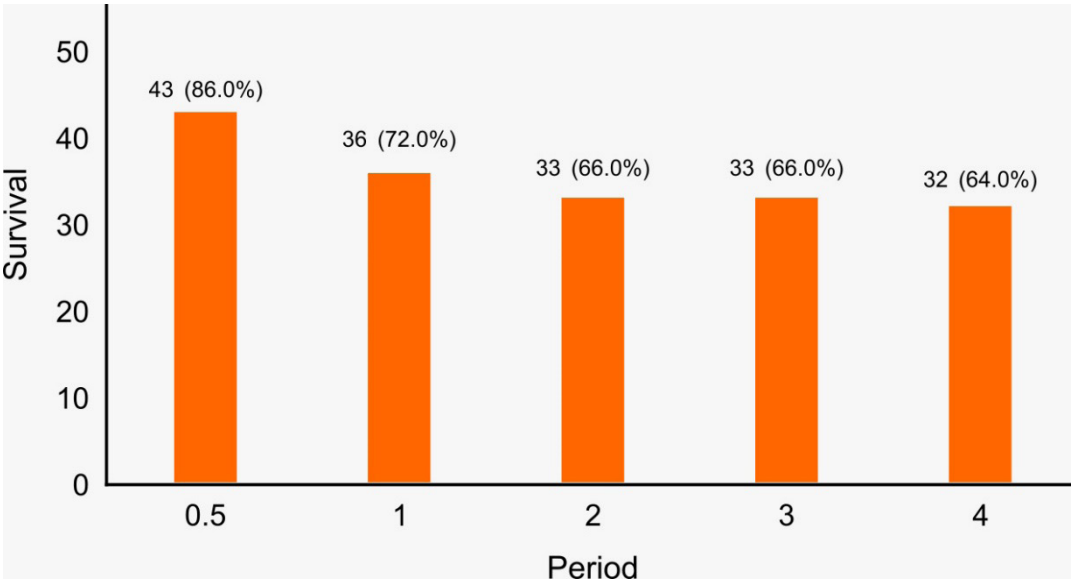

FIGURE 3. Overall survival of patients with osteosarcoma at the Departement of Anatomical Pathology, Sardjito General Hospital, Yogyakarta 2012-2020

TABLE 3. Kaplan Meier test

Variable	Expression	Event [n (%)]	Mean survival	p
CDK4	Negative	6 (50.0)	23.6	0.821
	Positive	12 (31.6)	23.4	

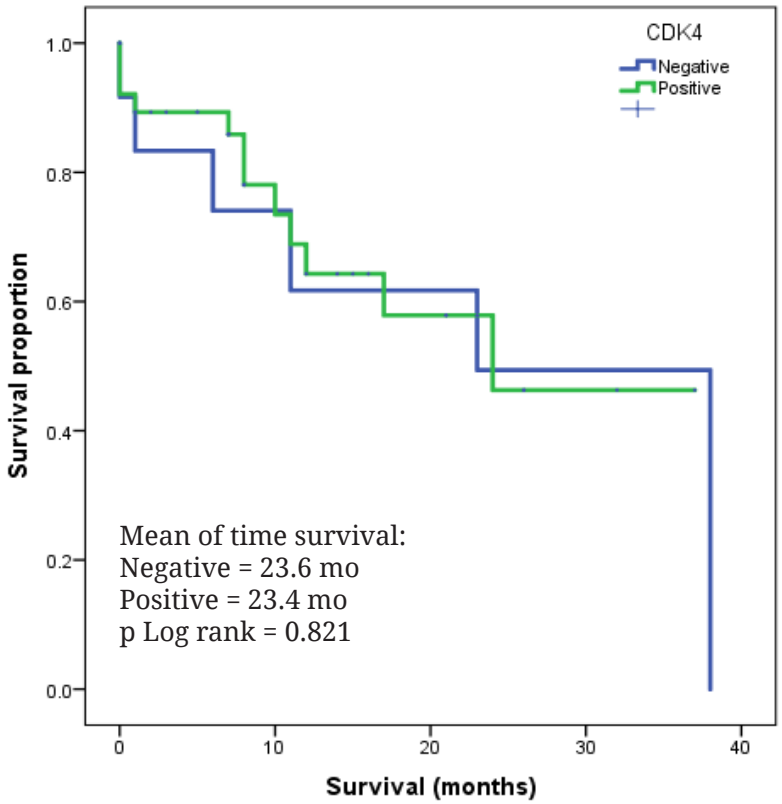

FIGURE 4. Kaplan-Meier curve of osteosarcoma patient survival based on CDK4 expression (positive and negative)

TABLE 4. Cox regression test

Variable	Expression	Univariate Cox regression		
		p	HR	95% CI
CDK4	Negative Positive	0.823	0.89	0.31-2.54

DISCUSSION

In recent years, CDK4 has been found to be a potential therapeutic target in several types of cancer, including human breast cancer, liposarcoma, glioblastoma, and melanoma. This finding has prompted the invention of a CDK4 inhibitor, considered a promising treatment for many types of cancer.[10] Jiang *et al.*[11] reported that CDK4 expression in tumor cell nuclei could be a potential marker for developing nasopharyngeal cancer and its poor prognosis. Zhou *et al.*[7] who were the first to determine the expression of CDK4 in osteosarcoma also reported that most of the osteosarcoma tissue is highly expressed CDK4, in which overexpression of CDK4 is associated with decreased survival rates. The CDK4 expression of the non-survivor samples was significantly higher than the CDK4 expression in the survivor samples. CDK4 can mediate cell proliferation and cell migration, affecting the progression of cancer, increasing the potential for metastasis, worsening prognosis, and affecting the response to chemotherapy; thus, it will be very promising if CDK4 inhibitor was developed as a treatment for osteosarcoma. It is hoped that using CDK4 inhibitors will improve the prognosis and survival of osteosarcoma patients.[7]

In this study, no significant relationship between CDK4 expression and all external variables, including sex, age, tumor location, histological grading, pathological staging, metastasis, and mortality was observed ($p > 0.05$). The survival of osteosarcoma patients for 6 mo; 1; 2; and 3 yr was 86.0; 72.0; 66.0; and 66.0%, respectively. This result was lower at 6 mo and 1 yr but higher at 2 yr and 3 yr in comparison to the results of a study at Shenzhen Second People's Hospital, which had an overall survival of 6 mo; 1 yr, 2 yr, and 3 yr of 96.87; 92.96; 61.71; and 42.18%, respectively.[12] The overall survival of this study is also lower than the results from other studies in other countries, with a relatively high 5-yr overall survival. EURAMOS (European and American Osteosarcoma Study) showed an overall survival of 79 and 71% for 3 and 5 yr, respectively.[13] Other than that, this study also has lower overall survival than a study in Taiwan, which showed a 5-yr survival rate of 67.7%.[14] This result is most likely due to therapy as Mirabello *et al.*[15] performed a clinical trial in the early 1980s, where chemotherapy administration before and after definitive surgical resection resulted in a significant increase to around 70% in the 5-yr survival rate.

Overall survival in the negative CDK4 group was 0.2 mo longer than the positive CDK4 group. However, it was not statistically significant ($p= 0.821$). Furthermore, CDK4 was also not significant predictor of mortality ($p= 0.823$). Overexpression of CDK4 does not significantly indicate a lower survival rate, and underexpression of CDK4 does not significantly indicate a higher survival rate. Some authors reported that complete resection of pulmonary metastatic lesions in patients with osteosarcoma and pulmonary metastases can help predict their survival. The survival rate is influenced not only by a single factor but also by a combination of other factors, including metastasis, tumor location, grading and staging, complications, and environments.[16]

CONCLUSION

In conclusion, CDK4 is highly expressed in osteosarcoma. However, the overexpression of CDK4 may not directly affect the survival rate in osteosarcoma. Other factors need to be considered to understand the complexity of the disease.

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The researcher states that it has no competing interests.

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Correlation between type of surgery and incidence of postoperative venous thromboembolism (VTE)

Supomo[1]*, Budi Mulyono[2], Usi Sukorini[2], Adika Zhulhi Arjana[3], Tandean Tommy Novenanto[4]

[1]Division of Cardiothoracic and Vascular Surgery, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, [2]Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, [3]Faculty of Medicine, Universitas Negeri Yogyakarta, Yogyakarta, Indonesia, [4]Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta

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ABSTRACT

Venous thromboembolism (VTE) is a significant complication in patients after undergoing major surgery. The type of surgery is believed correlated with the incidence of VTE. This study aimed to evaluate the correlation between type of surgery and incidence of VTE among patients who underwent major surgery. It was a retrospective study conducted in Dr. Sardjito General Hospital, Yogyakarta using medical record data of patients who underwent major surgery and were diagnosed with VTE between 2016 and 2020. Patients were grouped by surgery type, and length of stay (LoS). All caused deaths were also analyzed. Among 29,120 patients who underwent major surgery, 76 (0.26%) experienced VTE with females patients accounting for 75%. The mean age of the patients was 55 yr. All VTE cases had the mean LoS of 25 d. The highest proportion of patients who experienced VTE were patients who underwent tumor removal (67.0%) followed by trauma patients (18.4%). A significant difference in the incidence of mortality between the surgical groups was reported (p = 0.02). Post-cardiology had the highest risk of mortality (OR=7.46; 95% CI: 0.322 - 172.61) while age had the lowest risk of mortality (OR=1.01; 95% CI: 0.953 - 1.071). In conclusion, surgery type is correlated with the incidence of VTE. Surgery due to cancer and trauma has a higher risk of VTE compared to the others.

ABSTRAK

Tromboemboli vena (VTE) merupakan bentuk komplikasi nyata pada pasien setelah menjalani operasi besar. Jenis pembedahan diyakini berkorelasi dengan kejadian VTE. Penelitian ini bertujuan untuk mengevaluasi hubungan antara jenis pembedahan dan kejadian VTE. Penelitian ini merupakan penelitian retrospektif yang dilakukan di RSUP Dr. Sardjito, Yogyakarta menggunakan data rekam medis pasien yang menjalani operasi besar dan terdiagnosis VTE antara tahun 2016 hingga 2020. Pasien dikelompokkan berdasarkan jenis operasi, dan lama rawat inap. Semua penyebab kematian juga dianalisis. Di antara 29.120 pasien yang menjalani operasi besar, 76 (0,26%) mengalami VTE dengan pasien perempuan berjumlah 75%. Usia rata-rata pasien adalah 55 tahun. Semua kasus VTE memiliki rata-rata lama rawat inap sebesar 25 hari. Proporsi pasien yang mengalami VTE tertinggi adalah pasien yang menjalani pengangkatan tumor (67,0%) disusul pasien trauma (18,4%). Terdapat perbedaan nyata dalam hal kematian antara kelompok bedah yang dilaporkan (p = 0,02). Pasca kardiologi memiliki risiko kematian tertinggi (OR=7.46; 95% CI: 0.322 - 172.61) sedangkan usia memiliki risiko kematian terendah (OR=1.01; 95% CI: 0.953 - 1.071). Kesimpulannya, jenis operasi berkorelasi dengan kejadian VTE. Pembedahan akibat kanker dan trauma mempunyai risiko terjadinya VTE lebih tinggi dibandingkan tindakan bedah lainnya.

Keywords:
major surgery;
venous thromboembolism;
thrombosis;
cancer;
prophylaxis

*corresponding author: supomo.tkv@mail.ugm.ac.id

INTRODUCTION

Venous thromboembolism (VTE) is a condition that occurs when a blood clot forms in a vein. It includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Deep vein thrombosis occurs when a blood clot develops in the deep veins, usually in the large veins located in the legs or pelvis. Whereas, PE occurs when a part of the DVT clot detach from the vein walls and travel to the lungs.[1,2] Thrombotic occurs due to a decrease or insufficient in antithrombotic factors or an increase in coagulation factors. The thrombotic can be caused by abnormalities in the vessel walls or an increase in thrombogenic substances circulating in the bloodstream.[1]

The World Health Organization (WHO) reported an annual VTE incidence of 1-2 per 1000 individuals. The patient's age is reported as a major risk factor for VTE. Furthermore, women in their reproductive phase are at higher risk of VTE than other age groups. Those with a history of cancer or surgery are also at an increased risk of VTE[2]. Asian people demonstrate a lower susceptibility to develop VTE compared to Caucasians and African Americans. In Indonesia, a multi-center study disclosed that the incidence of DVT is between 37 and 40% among patients with acute medical illnesses.[3] This study just focused on the incidence rate of DVT, the type of surgery associated with VTE incidence has not been investigated, yet.

The incidence of VTE is affected by Virchow's triad, which includes stasis in blood flow, blood hypercoagulability, and damage to the vein endothelial. Immobilization due to surgery is a major risk factor for VTE. The surgeries lasting over 2 hr have a higher risk.[4] The immobilization inhibits the blood flow which triggers VTE development. As many as 15 to 30% of surgical cases lasting more than 2 hr without thromboprophylaxis cause VTE.[5] Coronary artery bypass surgery, major urological surgery, gynaecological surgery for cancer, major orthopedic surgery, and trauma are also associated with a higher risk of VTE.[6]

A minimum of 20 to 30 major operations are performed in Dr. Sardjito General Hospital, Yogyakarta daily which increases the risk of postoperative complications including VTE. This study aimed to evaluate the correlation between the type of surgery and the incidence of VTE among patients who underwent major surgery in Dr. Sardjito General Hospital, Yogyakarta. The results can inform the development of strategies to reduce the risk of VTE and to improve patient outcomes. The risk factors of VTE among patients who underwent major surgery were also evaluated.

MATERIAL AND METHODS

Design and subjects

This retrospective study was conducted in Dr. Sardjito General Hospital, Yogyakarta using medical record data to investigate the demographic conditions of patients who experienced postoperative VTE. The study was approved by the Health and Medical Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/ Dr. Sardjito General Hospital with reference number KE/FK/0612/EC/2022.

Procedure

Data between 2016 and 2020 were collected based on the ICD-10 diagnostic code recorded on venous thromboembolism (I80). Patients who underwent major surgery and were diagnosed with VTE were included in this study. Patients who had been diagnosed with VTE before undergoing surgery, pregnant women, and those with a history of blood thinner usage

or coagulation disorders before surgery were excluded. The subjects were then grouped based on the type of surgery, including oncology, cardiothoracic, vascular, digestive, genitourinary, and trauma. Length of stay and mortality that cause of death were also collected.

Statistical analysis

Kruskal Wallis was used to analyze differences among groups, Chi-square for categorical analysis, and Cochrane-Armitage test for trend assessment in the year. The association between risk factors and mortality was evaluated using a multivariable logistic regression model. Univariate analysis was performed first and then variables with p-value <0.25 was included in multivariate analysis in one-step analysis. All tests were considered significant with a p-value of <0.05. All statistical analyses were performed using MedCalc software version 19.6.

RESULTS

A total of 76 subjects (0.26%) among 29120 patients who underwent surgery experienced VTE. The number of female patients (75%) was higher than male subjects. The mean subject aged was 55 yr with the lowest age was 17 yr and the oldest was 85 yr. All VTE subjects had DVT in the lower limb. The mean length of stay (LoS) of the subjects was 25 d. The highest proportion of patients who experienced VTE were patients who underwent tumor removal (67%) followed by trauma patients (18.4%). There was no difference in LoS between the surgical group (p = 0.58). The longest median LoS was experienced by patients in the vascular group (34.5 d) while the fastest was in the trauma group (10 d) (TABLE 1).

The results of logistic regression analysis are presented in TABLE 2. A significant difference in the incidence of subject mortality between the surgical groups was reported (p = 0.02). However, no significant trend of surgery procedures between 21016 and 2020 was observed (p>0.05). The multivariate logistic analysis showed that post-cardiology subjects with post-cardiology has the highest risk of mortality (OR=7.46; 95% CI: 0.322 - 172.61) while age had the lowest risk of mortality (OR=1.01; 95% CI: 0.953 - 1.071).

TABLE 1. Characteristics of subjects by year

Variable	2016 (n=16)	2017 (n=12)	2018 (n=17)	2019 (n=18)	2020 (n=13)	Total (n=76)
Age [median (IQR) yr]	51 (36; 81)	51 (30; 73)	59 (18; 82)	55 (17; 71)	57 (41; 85)	55 (17; 85)
Male [n (%)]	3 (18.8)	4 (33.3)	4 (23.5)	7 (38.9)	1 (7.7)	19 (25.0)
Female [n (%)]	13 (81.2)	8 (66.7)	13 (76.5)	11 (61.1)	12 (92.3)	57 (75.0)
Surgery [n (%)]						
• Malignancy	12 (75)	7 (58.3)	11 (64.7)	13 (72.2)	8 (61.5)	51 (67.1)
• Cardiothoracic	0 (0)	1 (8.3)	1 (5.9)	0 (0)	0 (0)	2 (2.6)
• Vascular	1 (6.2)	2 (16.7)	0 (0)	2 (11.1)	0 (0)	5 (6.6)
• Abdominal	0 (0)	0 (0)	1 (5.9)	1 (5.6)	0 (0)	2 (2.6)
• Genitourinary	0 (0)	1 (8.3)	0 (0)	0 (0)	1 (7.7)	2 (2.6)
• Trauma	3 (18.8)	1 (8.3)	4 (23.5)	2 (11.1)	4 (30.8)	14 (18.4)
LoS [median (IQR) d]	24 (12; 38)	15 (9; 32)	18 (6; 56)	14,5 (5; 45)	16 (8; 32)	18 (5; 38)
Death [n (%)]	4 (25)	1 (8.3)	4 (23.5)	2 (11.1)	1 (7.7)	12 (15.8)

IQR: inter-quartile range; LoS: length of stay

TABLE 2. Logistic regression analysis

Variable	Univariate (OR; 95% CI)	Multivariate (OR; 95% CI)
Gender[1]	1.63 (0.431 - 6.190)	
Age	0.97 (0.93 - 1.014)	1.01 (0.953 - 1.071)
LoS	1.01 (0.987 - 1.042)	
Surgery[2]		
• Cardiothoracic	6.29 (0.351 - 112.460)	7.46 (0.322 - 172.608)
• Vascular	1.57 (0.153 - 16.183)	
• Abdominal	NA	
• Genitourinary	NA	
• Trauma	0.484 (0.054 - 4.298)	

[1]female as reference; [2]malignancies as reference

DISCUSSION

Venous thromboembolism remains a prevalent occurrence after surgery, particularly in major surgical procedures. It typically occurs as a complication stemming from conditions involving the formation of blood clots within deep veins. These clots can manifest in various veins, although they most frequently develop in the deep veins of the lower leg (DVT) or the lungs (PE).[2] The occurrence of symptomatic VTE within the initial month following surgery is approximately 2% for patients undergoing abdominal or pelvic surgical interventions.[7] Recent studies demonstrated that the risk of clotting in postoperative patients persists for at least 3 mo following the surgery.

The postoperative VTE is influenced by intrinsic factors inherent to the patient and extrinsic factors related to the surgical procedure. These extrinsic factors encompass elements like the duration of the surgery, the extent of immobility during the perioperative period, and the emergence of postoperative complications.[7,8] For instance, in non-oncologic general surgery cases, the median period until VTE occurrence was found to be 16 d.[8] The majority of these instances (77%) happened after the first week, and a quarter (25%) took place after 30 d. The incidence of VTE escalates after the discontinuation of prophylactic measures. This study showed that age and gender are not associated with the frequency of VTE occurrences. The average age of the patients was approximately 55 yr (17–85 yr). However, it is worth noting that age usually serves as a substantial risk factor for VTE. This is primarily due to increased blood coagulability, which is more prevalent in older people. Moreover, advanced age is linked to a higher occurrence of risk factors for VTE such as cancer, immobility, hospitalization, and surgery. Notably, around 75% of the post-surgery VTE cases in this study involved female patients.[9,10]

Gender also exerts an impact on VTE risk, with age-adjusted incidence rates being higher for men compared to women (130 per 100,000 versus 100 per 100,000 population). Nevertheless, in the younger adult population, women experience a slightly elevated annual VTE incidence due to hormonal factors like pregnancy, the postpartum period, and the use of oral contraceptives. The

use of external hormones, including oral contraceptive therapy, is linked to a 1.5-fold increased risk of incident VTE in women.[9,10] Pregnant and postpartum women face a notably higher VTE risk than those who are not pregnant, with the risk during these periods being up to 6 times greater. This risk amplifies as the pregnancy progresses, reaching up to 9 times higher in the third trimester. This heightened risk arises from physiological changes, including elevated clotting factors, reduced levels of available free protein S, and diminished fibrinolytic factors. Several other factors contribute to the risk of VTE during pregnancy and the postpartum phase, such as increased venous capacitance and pooling, physical compression of the left iliac vein, and immunological shifts. Risk factors for VTE during pregnancy and postpartum encompass caesarean section delivery, preeclampsia, and thrombophilia.[11,12] Additionally, disparities in VTE incidence have been observed among different race and ethnic groups. Hispanics and Asians exhibit notably lower rates compared to Caucasians or African Americans. For example, African Americans have a higher case-fatality rate for unexplained VTE. Furthermore, the likelihood of developing cancer-associated blood clots is lower in certain cancer types among Asian and Pacific Islanders compared with Caucasians (HR: 0.2–0.9).[13]

This study demonstrated that 67.1% of patients who underwent surgery were diagnosed with malignancy. Venous thromboembolism is a common complication in cancer patients, occurring as a result of various factors associated with the disease.[14] The pathophysiology of VTE in cancer patients involves a hypercoagulability mechanism. This mechanism can be attributed to the direct activation of procoagulant pathways by cancer cells or the indirect systemic effects of cancer on various cell types, including leukocytes, endothelial cells, and platelets. Cancer cells activate the procoagulant pathway through abnormal tissue factor expression, release of tissue factor-containing microparticles, and activation of other surface proteases. In certain cancers, neutrophils release neutrophil extracellular traps (NETs), which lead to procoagulant pathway activation and platelet activation. A bidirectional relationship exists between cancer and thrombosis, where increased tumor burden raises the risk of VTE, while VTE can serve as an indicator of tumor aggressiveness and poor prognosis.

Various tumor types increase platelet and leukocyte counts in the bloodstream, thereby raising the risk of venous thrombosis through the formation of NETs or release of tissue factor (TF). Tumors can also release extracellular vesicles (EVs) containing TF, polyphosphate, or podoplanin (PDPN). TF-containing EVs activate the blood coagulation process, polyphosphate-containing EVs activate factor XII (FXII) and platelets, while PDPN-containing EVs activate platelets. Additionally, tumors release plasminogen activator inhibitor 1 (PAI1), which inhibits fibrinolysis.[15]

Studies showed that cancer patients have a higher relative risk of developing VTE compared to the general population. Malignancy has been associated with almost 20% of VTE cases that are newly diagnosed. However, among these cancer patients small number as 8% were diagnosed with VTE within a year after cancer diagnosis, highlighting the need for early recognition and treatment of this condition in cancer patients.[16] Notably, VTE stands as the second leading cause of death among cancer patients, following the cancer itself. The incidence of VTE during hospitalization varies across different cancer types, with pancreatic and lung cancer patients having the highest risk. A previous study reported that pancreatic cancer patients have the greatest risk of hospitalization due to VTE, followed by lung cancer

patients. Increased tumor burden heightens the risk of VTE, while VTE can also serve as an indicator of tumor aggressiveness and poor prognosis in cancer patients.[17]

Various patient-related risk factors contribute to VTE development in patients with malignancy. These risk factors include advanced age, obesity, black ethnicity, and comorbidities such as infections, anemia, kidney disease, and lung disease. Identifying these risk factors is crucial for identifying high-risk cancer patients and implementing appropriate preventive measures.[18]

The incidence of VTE among cancer patients is 13.9 cases per 1,000 person/yr, while high-risk patients have an overall incidence of VTE rate of 68 per 1,000 person/yr. The risk of VTE ranges 4 to 7 time greater in patients with cancer than in the general population. As much as 20% of cancer patients experienced VTE. The first 12 mo after patients diagnosed with cancer have highest VTE incidence due to intensive therapies. However, the type of cancer is greatly associated the incidence of VTE. Certain types of cancers such as cancer of pancreas, brain, lung, stomach, and ovaries have a higher risk of the VTE incidence compared to the breast and prostate cancers. The risk of VTE is increased by hematological malignancies, particularly lymphoma. Furthermore, systemic chemotherapeutic treatment is also associated to an increased risk of VTE.[14,16,17,19]

Based on their characteristics and propensity to cause blood clots, certain cancer types are categorized as high risk or very high risk for VTE using the Khorana score and Vienna cancer and thrombosis study (CATS) score. Lung, gynecologic, lymphoma, bladder, and testicular cancer are categorized as high-risk tumors, whereas pancreatic and stomach tumors are categorized as very high-risk. Additionally, the degree of malignancy at the time of the first cancer diagnosis is associated with VTE. Metastatic cancer is a significant predictor of thrombosis.[20,21]

Cancer patients who undergo systemic chemotherapy drugs, antiangiogenic agents, and hormonal therapy are at a higher risk of developing VTE. As a result, thromboprophylaxis is often considered for these patients to prevent the occurrence of blood clots. While the thrombotic risk associated with immunotherapy is currently unknown, reports show that the incidence of VTE in cancer patients can be as high as 30%. Therefore, healthcare providers need to monitor cancer patients for signs and symptoms of VTE, especially during the first year after diagnosis or progression, and provide timely intervention to prevent this potentially life-threatening complication.[16,22]

The mortality rate reported in this study was 15.8% (TABEL 1), which is higher than reported in other studies. A greater number of patients with malignancy may be associated with this result. The higher mortality rates of VTE in cancer patients is associated with outpatient chemotherapy. The 1-year survival rate is lower for cancer patients with VTE (12%) than for those without VTE (36%).[23] The mortality rate was 26.4% among cancer patients and 4.1% among those without cancer.[24] Age > 80 yr, stage of malignancy, and previous incident of VTE are the strongest death predictor. However, the last predictor increased the mortality risk, regardless of the primary cancer site. Patients with cancer-associated thrombosis may die due to fatal thrombotic events or bleeding complications related to therapeutic anticoagulation, which are more common in malignancy patients.[25]

The majority of patients who develop VTE besides malignancy have undergone surgical procedures due to trauma (18.4%) or vascular problems (6.6%). Orthopedic and trauma surgeries, particularly total hip replacement (THR) and total knee

replacement (TKR), have a high risk of VTE development if thromboprophylaxis is not used, with up to 50% of orthopedic patients experiencing DVT. According to data from the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) from 2008 to 2016, the overall 30-d VTE rate was 0.6% for THR and 1.4% for TKR. Moreover, major thoracolumbar spine surgery has a PE prevalence of 0.88% and DVT prevalence of 0.66%, with a higher risk if surgeries involve more than 5 segments.[26,27]

It was also found that vascular surgery has a higher incidence of VTE compared to other surgeries. This is linear with a retrospective analysis of the ACS NSQIP. It was found that the incidence of DVT was higher among vascular surgery patients compared to general surgery patients, with rates of 0.99 and 0.66%, respectively. A study that compared LMWH and UFH as thromboprophylaxis found that patients undergoing aortic surgery have a higher incidence of DVT (7.5%) than those undergoing surgery for PAD (3.4%). Despite receiving thromboprophylaxis, patients who underwent major lower extremity amputation still had a relatively high incidence of DVT at 10.7%.[28-30]

Cardiothoracic surgery poses a significant risk for VTE, with an incidence of 2.6%. Patients undergoing major thoracic surgery are at even higher risk, with a 3.8% chance of developing VTE. The risk of developing DVT and PE after cardiothoracic surgery is 1.62 and 0.38%, respectively. A history of VTE, getting older, being obese, having left or right ventricular failure, being mechanically ventilated for an extended period, using a central venous catheter, and not using any anticoagulant or antiplatelet medications are all risk factors for VTE after cardiac surgery.[31-33]

The occurrence of DVT and PE during digestive surgery is expected to range from 2.75 to 8.9%, with colorectal cancer and inflammatory bowel disease being the primary risk factors. For liver resection and significant abdominal surgery without prophylaxis, the prevalence of VTE was 0.7 and 0.5%, respectively. The probability of developing DVT after significant abdominal surgery is most significant within the first two wk following the operation, while complications such as PE can manifest even later.[34-36]

Vein thromboembolism is uncommon during genitourinary surgery, with a DVT incidence of 5.54% in urologic procedures. Transurethral resection of the prostate or bladder tumor is a low-risk procedure for VTE, with reported incidence rates of 0.11 to 0.2% for DVT and 0.1 to 0.45% for PE. In contrast, open surgery for prostatectomy has a VTE incidence of 2.2%, while robotic-assisted laparoscopic procedures have lower incidence rates of 0.5 to 1.8%. The VTE incidence rates for radical nephrectomy, partial nephrectomy, and nephroureterectomy are 1.1, 1.0, and 1.9%, respectively. Despite these low incidence rates, extended thromboprophylaxis is typically recommended in urologic surgery.[37,38]

A study that evaluated the association between surgery duration and the risk of VTE in cancer patients was reported. Longer surgical procedures are linked to an increased risk of DVT in the lower extremities. Prolonged immobilization resulting from lengthy surgeries can cause blood stagnation, heightened coagulation, and damage to blood vessel endothelium. Patients undergoing lengthier surgeries are more likely to experience blood stagnation, hypercoagulability, and vascular trauma, all contributing to the development of VTE. Hence, longer surgical durations should be considered as a potential risk factor for VTE in cancer patients.[39]

The frequency of VTE events also varies depending on the LoS. A study by Amin *et al.*[40] reported that the highest

VTE occurrence during hospitalization within 6 mo after discharge was observed in patients with stays of ≥7 d, followed by those with stays of 4 to 6 d, and 1 to 3 d. The majority of VTE occurs within the first 40 d after admission, irrespective of the LoS. The cumulative VTE rate during this period also varies based on the LoS, with higher rates in patients with longer stays. For instance, the cumulative VTE rate during the initial 40 d after admission is 1.5% for patients with stays of 1 to 3 days, 2.3% for 4 to 6 d, and 6.6% for ≥7 d. This underscores the importance of assessing VTE risk and implementing appropriate prophylaxis in cancer patients with extended hospital stays to reduce the risk of severe VTE events.[40]

Patients undergoing major surgeries are advised to use both medicine-based and mechanical methods to prevent complications. Mechanical techniques are preferred if medication isn't used, with intermittent compression devices being a better choice than graduated compression stockings. To prevent VTE, it is recommended to combine mechanical and medication-based approaches rather than relying solely on medication. The choice to combine methods depends on the patient's risk of VTE and bleeding, as well as the specific surgery they're having. However, it's important to note that using inferior vena cava filters to prevent VTE in major surgery patients isn't recommended. When it comes to antithrombotic prophylaxis duration, using an extended plan is better than a short-term one. This means starting antithrombotic prophylaxis either soon after surgery or with a delay of up to 3 wk. The point where early and delayed antithrombotic administration is differentiated is the 12-hr mark after surgery. According to the recommendations from the American Society of Hematology, patients undergoing various surgical procedures should use medication-based prevention to reduce the risk of VTE. For individuals having total hip or knee arthroplasty, using aspirin or anticoagulants is suggested. In the case of hip fracture repair, it's advised to consider using low molecular weight heparin (LMWH) or unfractionated heparin (UFH). Generally, medication-based prevention is recommended for significant general surgeries, except for laparoscopic cholecystectomy and major neurosurgical procedures. For transurethral resection of the prostate (TURP), medication-based prevention is not recommended. However, considering LMWH or UFH might be appropriate for patients undergoing radical prostatectomy, major vascular or cardiac surgery, and significant gynecological surgery. Additionally, patients facing major trauma with a low to moderate risk of bleeding are advised to use medication-based prevention.[40,41]

This study has limitations. First off, the information used in this study came from a registry that tracks instances of symptomatic VTE. This suggests that we were missing data on surgery patients who were not affected by this specific consequence. We could have determined the occurrence rate for each event and compared the two groups if we had data on such cases. Due to the fact that all patients in the sample had VTE, we are unable to demonstrate a direct causal link between the use of prophylaxis and the prevention of VTE.

Furthermore, the registry does not collect information on variables like the length of the surgical process, the occurrence of further surgical problems, the urgency of the treatments, or the use of mechanical prophylaxis. Additionally, we didn't record information regarding the anesthetic type applied, the patient's comorbidity index, or any other elements that would have indicated how serious the patient's condition was. Last but not least, our analysis excluded gynecological and obstetric surgery, including as cesarean sections and other operations connected to gynecological cancers.

CONCLUSION

Vein thromboembolism is a common complication following surgery, and postoperative patients are at a persistent risk of VTE, which is influenced by intrinsic and extrinsic factors. Surgery type affects surgery duration, perioperative immobilization, and postoperative complications. Surgery due to cancer and trauma have a higher risk of VTE compared to other type of surgery, although the incidence of VTE may vary based on cancer type and malignancy extent at initial diagnosis. Combined prophylaxis with mechanical and pharmacological intervention is generally recommended based on individual patient risk of VTE and bleeding, as well as the type of surgical procedure.

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Association of fat mass and obesity associate (FTO) single nucleotide polymorphisms in the first intron and obesity risk among Indonesians

Benedikta Diah Saraswati[1], Luluk Yunaini[2]*, Dwi Anita Suryandari[2]

[1]Master's Programme in Biomedical Sciences, Faculty of Medicine Universitas Indonesia, Jakarta.
[2]Departement of Medical Biology Faculty of Medicine Universitas Indonesia, Jakarta

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ABSTRACT

Obesity is one of the global pandemics characterized by an excessive fat buildup due to disruption of energy homeostasis in the body. As obesity is a risk factor for many other non-communicable diseases such as diabetes and coronary heart disease, it is crucial to understand the risk factors that contribute to the pathogenesis of obesity. Although obesity is mainly caused due to unhealthy lifestyles, genetic predisposition also plays a part in the pathogenesis of obesity. Individuals who carry risk alleles for genes that control energy balance in the body have a greater risk of developing obesity. Fat mass and obesity associate (FTO) is a gene strongly correlated with obesity and is widely expressed in the hypothalamus. This gene is predicted to have 89 common variations that affect obesity-related phenotypes. Among Indonesians, the three most studied single nucleotide polymorphisms (SNPs) in the first intron of the FTO gene are rs1421085, rs17817449, and rs9939609. They are strongly associated with obesity's related traits such as weight gain, fat mass, body mass index (BMI), waist, and hip sizes. rs993609 is the most studied among diverse ethnicities in Indonesia, with AA genotype and allele A as a risk allele.

ABSTRAK

Obesitas termasuk ke dalam salah satu permasalahan global yang didefinisikan sebagai dengan adanya penimbunan lemak berlebih akibat terganggunya homeostatis energi pada tubuh. Obesitas merupakan faktor risiko dari berbagai penyakit seperti diabetes melitus, jantung, dan berbagai jenis kanker. Oleh sebab itu pengetahuan mengenai etiologi dari obesitas penting untuk diteliti, termasuk perihal mencari faktor genetik yang sekiranya terlibat dalam patogenesis obesitas. Walaupun bersifat poligenik, individu yang memiliki alel risiko untuk gen yang terlibat dalam mengontrol keseimbangan energi dalam tubuh memiliki risiko lebih besar terkena obesitas. FTO diketahui berkorelasi kuat dengan obesitas dan diekspresikan secara luas di hipotalamus. Gen ini diperkirakan memiliki 89 variasi umum yang memberikan berbagai efek pada fenotipe terkait obesitas. Pada populasi di Indonesia, tiga *single nucleotide polymorphisms* (SNP) yang paling banyak dipelajari pada intron pertama gen FTO adalah rs1421085, rs17817449, dan rs9939609. Ketiga titik tersebut sangat terkait dengan sifat terkait obesitas seperti penambahan berat badan, massa lemak, indeks massa tubuh, lingkar pinggang, dan ukuran pinggul. rs993609 adalah titik yang paling banyak dipelajari di antara beragam etnis di Indonesia, dengan alel A dan genotipe AA sebagai faktor risiko terhadap obesitas.

Keywords:
obesity;
FTO;
risk alleles;
SNP;
polymorphisms

INTRODUCTION

Obesity can be defined as abnormal and excessive fat accumulation that may impair health with a body mass index (BMI) of more than 30 kg/m^2. Because of its high prevalence in many countries, the World Health Organization (WHO) classified obesity as a global pandemic.[1] Obesity is the risk factor of many non-

Corresponding author: luluk.yunaini@ui.ac.id

communicable diseases, especially coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia, and stroke, thus indirectly leading to death.[2] The WHO predicted about 2.8 million adults in 2018 die from being overweight or obese.[3] Most deaths are caused by diabetes, ischemic heart disease, and the increased risk of cancer from being overweight or obese. Indonesia is one of the top nations with the highest obesity-related cancer death rates.[4]

Obesity is caused mainly by a discrepancy in energy intake and expenditure. The intake of energy-dense meals high in fat and carbohydrates and a lack of physical exercise has increased due to more sedentary lives and poor diets.[5] Moreover, genetic factors also play a part in obesity pathogenesis. It is believed that about 5% obesity in children due to that runs in the family.[6]

According to Genome-Wide Association Studies (GWAS), since 2006, more than 50 genes and 300 single nucleotide polymorphisms (SNPs) have contributed to obesity's incidences and traits.[7] Of all these genes, FTO, which encodes fat mass and obesity associate (FTO), is estimated to have the most remarkable association with obesity incidences in various countries worldwide.[8] Fat mass and obesity associate is a dioxygenase enzyme that plays a role in repairing alkylated DNA and RNA. Overexpression of FTO can influence the expression of m^6A-dependent transcription factors to control preadipocyte differentiation.[9] Fat mass and obesity associate has 89 common variations that exert various effects on obesity-related phenotypes.[8] Single nucleotide polymorphisms rs1421085, rs8050136, and rs9939609 are among the most studied variations in an increased risk of obesity. These three variations are associated with various parameters related to obesity, such as weight gain, fat mass, body mass index (BMI), and waist and hip size.

It is important to mention that FTO's polymorphisms have been related to obesity and being overweight in Asian, African, Hispanic, and Native American populations, in both adults and children, suggesting that FTO polymorphisms significantly influence obesity.[10] Indonesian, a broad and multicultural populations from the crossing point of Asia and the Pacific, is the source of genetic diversities.

MATERIAL AND METHODS

This paper aimed to assess the possible mechanism of how the FTO gene interactions with other energy-regulating genes will contribute to the pathogenesis of obesity. This paper also discuss FTO's common intronic variations (rs1421085, rs8050136, and rs9939609) associations with obesity-related traits and their possible mechanism, especially in the Indonesian population. Hence, the reviewer searches for some research journal articles from 2009 and above published through electronic databases as part of the review process. Among other electronic databases, Google Scholar, PubMed, and ResearchGate were used. The keywords "Obesity gene FTO", "FTO SNPs related to obesity", and "FTO variants in Indonesian" were used to search the articles needed to write this review.

A total of 67 articles were used to write basic theories of FTO gene and their SNPs located in the first intron. Journals were identified based on the following inclusion criteria: 1) full-text articles published in English or Bahasa; 2) able to address the role of the FTO in etiology of obesity; 3) had enough information regarding how FTO and its variations interact with environment to affect how obesity manifests itself. Especially for the purpose to show FTO first intron SNPs' possible effects in Indonesian population, we used any data available online with following criteria: 1) SNPs located on the first intron of FTO, 2) had and effects towards obesity and

obesity related symptoms and diseases and 3) using Indonesian population aged range from adolescent to adult. For a summary of FTO first intron SNPs among Indonesian we used a total of 9 articles.

RESULTS

Etiology and pathogensis of obesity

Numerous factors contribute to obesity. Obesity, rather than solely emerging from the passive deposition of extra weight, appears to be a disease of the energy balance system. Obesity is caused by two different but linked processes: a prolonged positive energy balance and resetting the body weight "set point" to a higher number.[11] Obesity is mainly caused by the environment or behavior, including excessive energy-dense food consumption and physical inactivity. Pathological overeating and physical inactivity appear to be connected with altered brain circuits and neuroendocrine feedback that lead to obesity.[12] The link between obesity and energy homeostasis is significantly influenced by the adipocyte hormone leptin, which circulates at concentrations proportionate to body fat mass.[11] Dietary variables contributing to the development of obesity include eating a high-fat diet, consuming large amounts of sugar-sweetened beverages, and the predominance of a wide variety of food at the markets. The other key factor in the etiology of obesity is reduced energy expenditure relative to calorie intake.[13] However, Obesity as a multifactorial disease results from the interactions of environmental and genetic variables.

Although genetic factors alone are unlikely to account for the rapid rise in obesity prevalence, it is believed that some genetic influences increase the risk of obesity brought on by environmental impacts in ways that favor positive energy balance (higher calorie intake, decreased physical activity, or both) and/or result in the biological defense of increased fat mass.[11] Genetic factors that may lead to obesity in a variety of ways, generically categorized as: 1) Single gene mutation on the leptin-melanocortin pathway, which is the key site for monogenic causes; 2) Obesity with additional characteristics, such as neurodevelopmental disorders and other organ/system anomalies, is referred to as syndromic obesity; 3) polygenic obesity which includes a significant number of genes together contribute to polygenic obesity, which is exacerbated by an environment that promotes weight gain.[14]

Monogenic mutations are single-gene mutations that produce a variety of rare forms of obesity. These mutations have been found in genes that code for the hormone leptin, the leptin receptor, pro-opiomelanocortin, and the melanocortin-4 receptor, all of which are involved in appetite control, food intake, and energy balance.[14] Various studies have found mutations in several alleles that have the predisposition to trigger obesity. In addition, human body weight and disposition are believed to be regulated by various genes. These genes include the obesity (OB), diabetes mellitus (DB), and FTO. The OB is associated with the secretory process of the hormone leptin, while the DB encodes the leptin receptor. Someone with mutations in OB and DB mostly experiences obesity problems.[3]

About 835 gene loci and 317 SNPs are associated with obesity, including FTO, MC4R, GNPDA2, TMEM18, NRXN3, SEC16B TNNI3K, QPCTL, and BDNF loci.[15] Among these loci, FTO is thought to have the most significant association with obesity in various countries globally. FTO was only known for its role in the pathogenesis of obesity; through the genome-wide analysis study (GWAS) in 2007, it was found that various variations in the FTO gene turned out to be associated with obesity in individuals with European ancestors.[16] People who have one of these gene variations have a greater risk of obesity and other obesity-

related traits than those who do not.

The first large-scale GWAS for quantitative BMI and height in East Asian ancestry populations showed that the FTO locus, which has long been recognized as a critical contributor to polygenic obesity in European people, also had the strongest connection result.[17] Following the GWAS meta-analysis, FTO variations are also relevant in many Asian ethnicities, including Singaporean, Malay, and Asian-Indian.[18] Thus, variations in the FTO locus are among the strongest candidates to be studied in the Indonesian population because there is a similar genetic distribution among the Malaysian and Singaporean people. However, a large-scale GWAS study using Indonesian ancestry has yet to be done.

The physiological function of FTO

Fat mass and obesity associate is encoded by the *FTO* gene, located on chromosome 16q12.2. This locus is from 53,737,875 bp to 54,155,853 bp of chromosome 16 and consists of 9 exons.[19,20] Bioinformatics analysis showed that FTO is a Fe(II) and 2-oxoglutarate-dependent oxygenase, characterized by a site for nucleic acid demethylation.[21,22] Although FTO is often associated with the risk of obesity, this gene's primary physiology function in humans remains unknown other than restoring damaged DNA and RNA by the demethylation process. Duplication of the FTO gene region causes mental retardation, obesity, and other disorders.[23]

Animal studies have shown a correlation between FTO and other hunger hormones like leptin. Still, no evidence supports the idea that human FTO *expression* is regulated at the transcriptional level in a leptin-dependent manner.[23] However, it is believed that FTO alters hypothalamic nuclear factor-kappa β (NF-κβ) signaling, impacts the metabolic consequences of a high-fat diet and requires leptin resistance induced by high-fat eating.[24] Leptin itself is known to suppress appetite, although the impact appears to be indirect. FTO and its neighbor gene RPGRIP1L are predicted to be coregulated because they share the same CpG island. RPGRIP1L is known to regulate leptin production.[25]

Fat mass and obesity associate is a crucial regulator in energy management. Fasting/feeding cycles regulate the expression of the FTO, which is strongly expressed in the hypothalamus. This geographical expression pattern is remarkable because the hypothalamus controls energy balance and food intake control.

Fat mass and obesity associate is also implicated in the adipogenesis process.[26] Adipocytes accumulate excessively in the adipose tissue of obese people. Fat mass and obesity associate mRNA levels in subcutaneous adipose tissue were shown to have a positive relationship with BMI, with greater levels of FTO mRNA in obese persons' fatty tissues.[27] Fat mass and obesity associate is involved in the development of obesity by affecting the level of hormones that control eating behavior or other molecules related to adipogenesis. Animal studies show that fto directly affects fat mass and, as a result, is likely to have a role in human obesity.[28] Fat mass and obesity associate protein has an oxidative demethylation activity towards N^6-methyladenosine (m^6A), the most common mRNA alteration in humans and mice considered involved in mRNA stability, splicing, and translation control.[22]

By influencing the m^6A level around the splice site of the adipogenic regulator, RUNX1T1, FTO contributes to modulating adipose cell differentiation.[27] Fat mass and obesity associate influences adipogenesis by controlling the mitotic clonal expansion (MCE). It is required for adipocyte differentiation within 48 h of adipogenic stimulation.[9] Overexpression of the FTO gene is

known to activate adjacent genes involved in energy balance and white adipocyte development.[29] After FTO has been identified as an obesity-associated gene via GWAS, many discoveries found that several variations in the FTO's first intron may be linked to obesity and other obesity characteristics.[23]

Overexpression of FTO increased m^6A demethylation, thus increasing the ghrelin mRNA level simultaneously. Ghrelin can only be synthesized after FTO demethylates m^6A.[30] The synthesized ghrelin will then penetrate the blood-brain barrier to exert its effect on the hypothalamus to increase appetite. According to research conducted in animals such as mice, the FTO gene might be a significant target for early dietary programming.[31,32] FTO is thought to affect the central nervous system's global energy sensors by interacting with mammalian target of rapamycin (mTOR), 5'-Adenosine monophosphate-activated protein kinase (AMPK), and uncoupling protein 2 (UCP2) (FIGURE 1).[23]

According to studies on mouse embryonic fibroblasts, cells with FTO-overexpression are resistant to amino acid shortages. Obesity is believed to be influenced by FTO's downstream mammalian target of rapamycin complex 1 (mTORC1).[28] mTORC1 controls the metabolism of glucose and glutamine, as well as the primary carbon sources used by mitochondria. It is known as a target for various hormones that play a role in regulating energy balance, such as leptin and ghrelin.[33] Fat mass and obesity associate is also controlled by the CUX1 transcription factor that governs leptin receptors' traffic, which modulates eating behaviour.[34]

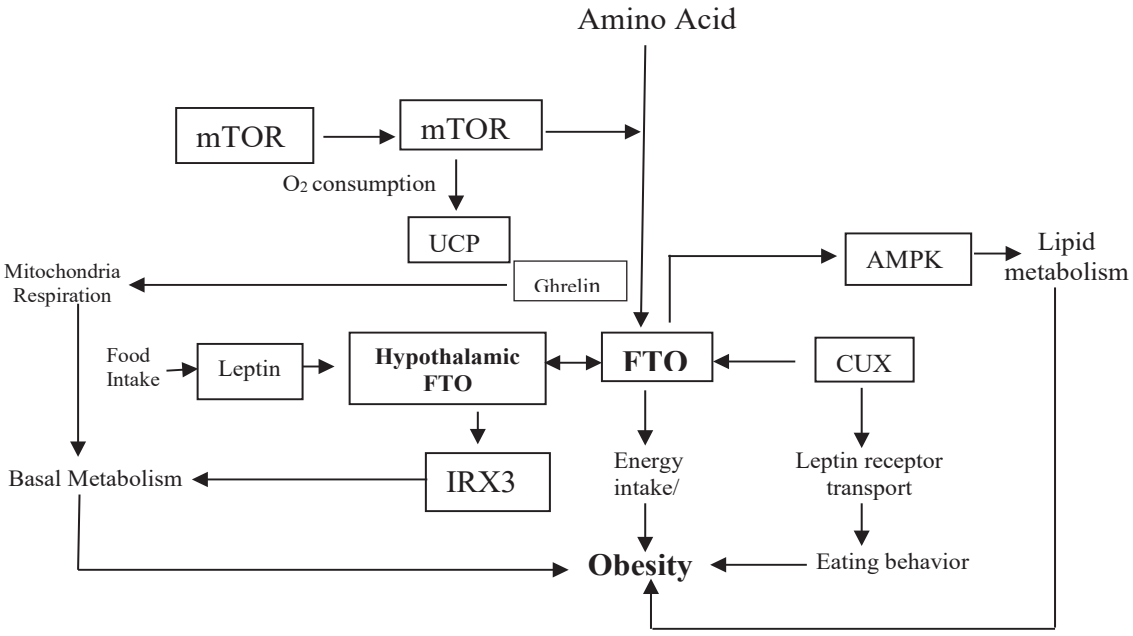

FIGURE1. Possible mechanism of how FTO causes obesity by interacting with other components. Fat mass and obesity associate is predicted to interact with hormones that regulate food intake such as ghrelin and leptin. In addition, FTO also plays a role in amino acid sensors through the mTOR signaling pathway. Adapted from Zhou *et al.*,[20] Abbreviation mTOR: mammalian target of rapamycin, UCP: uncoupling protein, CUX: Cut Like Homeobox, AMPK: 5' AMP-activated protein kinase, IRX3: Iroquois homeobox 3.

By modifying the expression of lipid-related genes, FTO-mediated m6A demethylation controls lipid metabolism and diseases associated with lipid disorders. Skeletal muscles' ability to consume lipids is restricted by FTO-dependent m^{6}A demethylation, which inhibits the AMPK pathway.[35] AMPK is a critical cellular energy sensor activated when cellular AMP levels rise. AMPK activation conserves energy for the cell under food deprivation by phosphorylating many substrates to inhibit anabolic activities, boost catabolic ones, transmit signals to mTORC1 and slow cell development.[36]

First intron variations of FTO and their association with obesity and other obesity's traits

Human obesity risk is related to genetic polymorphisms in non-coding regions of the FTO locus, which have small but statistically significant impacts. It is predicted that the possible mechanism by which these non-coding variations increase obesity risk is mediated through effects on adjacent genes that alter brain development and the formation of beige adipose tissue.[37] It was shown that individuals with the obesity-promoting FTO variation were 23% more likely to be obsessed than those without.[38] On the other hand, physical exercise has been shown to reduce the risk of obesity, with active persons with the obesity-promoting gene having a 30% lower risk than sedentary adults.[11] Fat mass and obesity associate SNPs, primarily located in the first intron, have been associated with individual variation in appetite rating scales, loss of control, bulk eating, and eating without hunger (FIGURE 2).[23]

As mentioned above, FTO and RPGRIP1L have co-regulation mechanisms. Besides sharing the same CpG island, there is an overlapping regulatory region inside FTO's first intron with at least two putative transcription factor binding sites (CUX1), one of which coincides with other obesity-related SNPs.[39] Thus, the possibility that changes in both FTO and RPGRIP1L mediate the link between FTO SNPs and body weight control expression.[16]

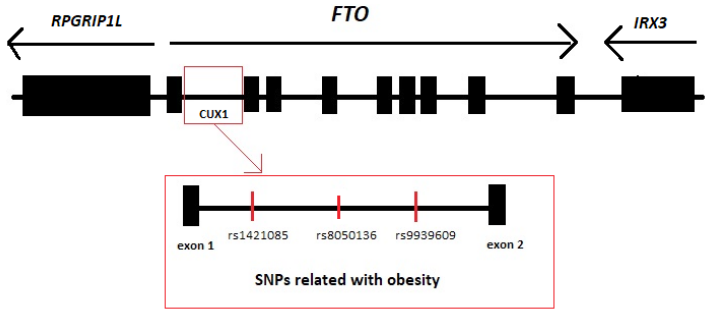

FIGURE 2. This paper reviewed the construction of the FTO gene structure and the location of the first intron SNPs. Fat and mass obesity associate is located on chromosome 16q12.2. A GWAS found a link between a common variant in single nucleotide polymorphisms in FTO's first intron with obesity. Three of the most studied SNPs are shown in this figure.

Another possible mechanism is by affecting the expression of IRX3, which plays a role in the differentiation process of adipocyte cells. These interactions are essential in regulating feeding behavior and detecting cellular nutritional status. Polymorphisms in the first intron of the *FTO* are strongly linked to increased BMI. Variations of FTO have also been linked to increased body fat composition, metabolite parameters, and metabolic diseases, including type 2 diabetes mellitus (T2DM).[40] Because the relevant risk alleles are relatively common, they are predicted to be responsible for many obesity cases in almost all human populations, especially among Europeans.[29]

Several studies show that some FTO polymorphisms may enhance calorie intake while decreasing satiety, resulting in weight gain. The mechanisms underlying the association between those variations with obesity are thought to be related to :1) the direct effect of FTO function in controlling body fat mass or 2) the presence of a non-random association (disequilibrium linkage) between the variant alleles tested with other causative changes in different alleles, which is still in the same area as FTO gene locus.[23]

Despite progress made, the actual mechanism by which SNPs in FTO impact human body mass remains unknown but is predicted to correlate with appetite and whole-body energy expenditure circuits in the brain and peripheral energy expenditure pathways. Most FTO expression variation is attributable to cis-regulatory variation in this gene's first intron.[41] Variations of the FTO gene in the first intron include rs9939609, rs1421085, rs17817449, rs9939973, rs1121980, and rs8050136. These FTO variants are in one cluster on the first intron of the FTO gene. All FTO variants identified by GWAS have a linkage disequilibrium (LD) of $r^2 > 0.80$, which indicates that the alleles are correlated, thus having almost the same significance level for obesity.[16] Among them, rs1421085, rs8050136, rs9939609, and rs17817449 were the most associated with obesity status and measures of obesity.

The effect of FTO polymorphism varies from one population to another. Ethnic variations in FTO allele frequencies, population sampling and age, and underlying patterns of significant environmental exposures might explain these inconsistencies.[27] This review specifically summarized all the first intron SNP of FTO using a population from Indonesia. Those variants and their association with obesity characteristics such as increased BMI, waist-hip ratio (WHR), waist circumference (WC), visceral fat accumulation (VFA), as well as metabolic abnormalities related to obesity such as T2DM, in Indonesian populations are summarized in (TABLE 1).

TABLE 1. FTO 1st intron's SNPs and their effect in obesity phenotype among Indonesians

rsID	Study population	Cases/controls	Genotype	Effects	Ref.
s9939609	Adult aged 19 –59 yr in Jakarta	40/40	AT/AA	Higher risk to obesity and tendency to consume excessive dietary fat	42
	Adult aged 20–30 yr in Jakarta	38/40	AA	increased visceral fat deposition with significantly higher WC, WHR, and VFA in males	43
	Balinese adults from both urban and rural area	612 cases	AA	Tendency to higher BMI, particularly in in rural and female population	44
	Chinese or Bataknese children (6-12 y.o., both sex)	Bataknese: 56/61 Chinese: 49/46	TT	Higher risk to Obesity in Chinese children but not in Bataknese children.	45
	Minangkabau's Adolescent girls	130/145	AA/AT	Tendency to eat more fried food and less fruit	46
	Minangkabau Women (25-60 y.o. with BMI under 40 kg/m^2)	133 non-obese women	AA/AT	higher BMI	47
rs1421085	Balinese adults from both urban and rural area	612 cases	CC	Higher BMI, particularly in females	44
	Javanese adults in Yogyakarta	94/94	CC	Increased the risk of and percentage of total body fat only in male subjects	40
	Adults aged 19 –59 yr in Jakarta	40 cases and 40 control	TC/CC	higher BMI and dietary fat food	48
rs8050136	Minangkabau Women (25-60 yr) with BMI (under 40 kg/m^2)	133 non-obese women	AA/AC	higher BMI	47

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, a waist-hip ratio; and VFA, visceral fat area

rs9939609

The minor allele for the FTO rs9939609 significantly enhanced the risk of obesity.[49] Variation in FTO (rs9939609) was the most strongly linked locus in a GWAS for BMI in 7,861 Koreans.[50] In Malay ethnicity living in Singapore. rs9939609 strongly related to obesity traits.[51] rs9939609 is positively correlated with increased calorie intake in adults. Individuals with the AT or AA genotypes consumed foods with higher calories than individuals with the TT genotype in individuals of Caucasian ethnic descent in Europe. However, the same thing also happened to other ethnicities in South East Asia, including races in Indonesia.[52]

Daya *et al.*[42] found that the risk allele A (AT or AA) at rs9939609 could modulate the consumption preferences of high-fat foods in the adult population. Susmiati *et al.*[46] tried to link the association of rs9939609 with a person's food preferences. It is estimated that the risk allele A at rs9939609 is thought to interfere with circulating levels of the hormone acyl-ghrelin. Increased

circulating ghrelin will inappropriately repress leptin production, which causes the body to feel hungry and increases the desire to consume high-calorie foods.[30]

Priliani *et al.*[44] found that the AA genotype also had a higher BMI than other genotypes in the Balinese population, especially in women and rural populations. This was predicted due to eating behavior and different body composition between women and men.[33] A diminished resting energy expenditure (REE) in the A allele of FTO might be the plausible reason it had a higher BMI than the TT genotype.[53] FTO rs9939609 also had high linkage disequilibrium with IRX3. IRX3 disturbed energy balance by directly inhibiting white adipose tissue browning. As a result, FTO rs9939609 Increased IRX3 expression may reduce energy expenditure and enhance fat storage if a risk allele is present.[54]

However, Lubis *et al.*[45] reported that the distribution of AA homozygote for the rs9939609 FTO gene was lower in the case group than in the control group compared to the TT genotype in a North Sumatera population of Chinese origin.[45] It was found that children with the AA genotype may be less likely to gain weight, whereas those with the TT genotype may gain weight more easily. Nevertheless, more study is needed to determine if the two alleles play distinct roles, such as one predisposing and the other protecting, or whether one of the two alleles causes function gain or loss. These inconsistencies might be due to variations in ethnic groupings, sample sizes, physical activity, and environmental exposure. According to a meta-analysis by Kilpelainen *et al.*[55] using 200.000 adults and about 20.000 children participants, 27% of subjects with these FTO variations most consistently related to obesity could reduce their risk through physical exercise.[55]

rs1421085

The genotypes CC and CT/CC of rs1421085 were linked to 59% and 71% higher odds of childhood obesity in Chinese children aged 3-6 years old.[56] The BMI growth in the Korean population was revealed to be highly correlated with the rs1421085 C allele.[57] rs1421085 correlated with an increase in BMI in Indonesia's Balinese population, with homozygous CC individuals having an approximately 1.12 kg/m^2 higher BMI than other genotypes.[58] This finding is similar to Cha *et al.*[59] also found that individuals in the Korean population who carry the C risk allele are known to be significantly associated with increased BMI. The increase in BMI is predicted to be caused by an unhealthy diet. Individuals with the rs1421085 variation with the C allele tend to have an eating behavior disorder known as binge eating or huge portions. Other parameters such as waist and hip size were also bigger in individuals with the C risk allele.

The *FTO* SNP rs1421085 (T> C) is known to have an enhancer element of the *IRX3* gene. Fat mass and obesity associate directly plays a role in adipocyte cells' biological activity by activating the thermogenin cascade in the browning process of fatty cells. It causes differentiation from the energy-dissipating beige adipocytes to energy-storing white adipocytes, followed by a decrease in the thermogenesis process, increased triglycerides in the blood, and increased storage of body fat reserves. The regulatory connections between FTO SNPs and IRX3 expression were also supported because alterations in the rs1421085 risk allele (C allele) caused a two-fold production of IRX3 and IRX5 in the early stages of adipocyte development by disrupting the ARID5B repressor's conservative motif.[60]

rs8050136

Meta-analysis from 2404 cases and 5713 control subjects showed that rs8050136 was significantly associated with obesity risk in East Asia populations.[61] A study in the Han Chinese population showed that rs8050136 is a risk factor for T2DM but independent of BMI.[62]

In Indonesia itself, using Minangkabau ethnicity groups, rs8050136 risk allele A is known to have a higher BMI than allele C. Like other studies covering different populations, this SNP is also associated with T2DM among the same ethnicity in Padang, Indonesia, one of the obesity-related diseases.[63]

rs8050136 mutation causes a change in factor binding Cut-like Homeobox 1 (CUX1) transcription and later decreases the expression of both FTO and RPGRIP1L in the hypothalamus. This risk allele (A allele) also can affect the expression of the RPGRIP1L, located FTO, by providing a regulatory element on the promoter part RPGRIP1L <100 bp from the FTO, by providing a regulatory element on the promoter part RPGRIP1L, which later acts as a repressor.[26] RPGRIP1L plays a role in controlling the leptin signaling process in the hypothalamus.[64] This caused a reduction of the leptin signaling process, thereby increasing the risk of obesity.[62]

rs17817449

FTO SNPs rs17817449 show the highest significant connection with BMI among people of Chinese descent, according to a large-scale meta-analysis focusing on GWAS investigation of East Asian populations. However, no research has been concluded using the Indonesian people, so this SNP is not discussed further in this review.

In our investigation, some potential limitations should be taken into account. First, not all of the studies SNPs in the first intron of FTO are included in this review. Other than that, there is still little research that examines the relationship of the first intron variation of FTO with the risk of obesity in Indonesia. Also, if variables like gender, age, food preferences, and lifestyle were changed, a more accurate analysis should also be considered. Additionally, there are discrepancies in results between ethnic groups due to different lifestyle interventions, different target populations (for instance, in terms of age group), surveying different polymorphisms in multiple research, and ignoring additional genetic factors that affect obesity.

CONCLUSION

SNP rs1421085, rs8050136, and rs9939609 were the most studied variations in an increased risk of obesity study in the Indonesian population. The most studied FTO SNP for obesity risk among diverse ethnicities in Indonesia is rs9939609 with risk allele A. Nevertheless, further data from a broader population and ethnic groups in Indonesia is needed to determine the impact of the first intron SNP of the FTO on obesity risk among Indonesians. It is essential to remember that even if FTO is the most promising among other candidate genes, it is only responsible for a small portion of obesity predisposition caused by genetic factors. Gaining a better understanding of how the FTO polymorphism impacts the body's fat mass can aid in the pathophysiology of obesity and the possible application of *FTO* inhibitors for obesity treatments.

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Reversible total atrioventricular block in a very high-risk non-ST-elevation myocardial infarction (NSTEMI) during conservative treatment in a limited resource setting: a case report

Susanti Mareta Anggraeni*, Ruth Grace Aurora
Jailolo General Hospital, North Maluku, Indonesia
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ABSTRACT

Total atrioventricular (AV) block is the most common type of conduction disorder found in acute coronary syndrome (ACS), which requires timely recognition and treatment. This case report aimed to present conservative medical treatment for managing total AV block (TAVB) in a very high-risk non-ST-elevation myocardial infarction (NSTEMI) in a rural area. We reported a patient with TAVB in a very high-risk NSTEMI. The patient was hemodynamically unstable and needed immediate percutaneous coronary intervention (PCI). Due to limited facilities and difficult access to immediate PCI, the patient was treated conservatively with the NSTEMI protocol. Epinephrine, as a β-adrenergic agonist, was administered to improve hemodynamic status. During conservative treatment, TAVB was converted into the first-degree AV block on the third day of intensive care. In a setting where revascularization strategies and pacemaker implantation are not feasible, administration of antithrombotic agents and β-adrenergic agonists can be considered to manage TAVB with NSTEMI with close monitoring.

ABSTRAK

Blok atrioventricular (AV) total merupakan bentuk gangguan konduksi jantung yang paling sering ditemukan pada kasus sindrom koroner akut (SKA). Laporan kasus ini bertujuan menjabarkan tatalaksana konservatif yang dapat dilakukan pada kasus blok AV total pada infark miokard akut non-segment ST elevasi (IMA-NEST) dengan risiko sangat tinggi di rumah sakit dengan fasilitas terbatas. Kami melaporkan pasien dengan blok AV total pada IMA-NEST dengan risiko sangat tinggi. Pasien datang dalam keadaan hemodinamik tidak stabil dan memerlukan akses untuk intervensi koroner perkutan (IKP) segera. Oleh karena keterbatasan fasilitas dan sulitnya akses untuk IKP segera, dilakukan tatalaksana konservatif dengan protokol IMA-NEST. Kami menggunakan epinefrin sebagai agonis **β**- adrenergik untuk memperbaiki status hemodinamik pasien. Selama perawatan konservatif tersebut blok AV total terkonversi menjadi blok AV derajat 1, yaitu pada perawatan intensif hari ketiga. Pada kondisi revaskularisasi dan pemasangan alat pacu jantung tidak dapat dilakukan, pemberian antitrombotik dan agonis **β**-adrenergik dapat dipertimbangkan sebagai terapi konservatif pada pasien blok AV total dengan IMA-NEST.

Keywords:
case report;
conservative treatment;
non-ST-elevation myocardial infarction;
total AV block;
β-adrenergic agonists

INTRODUCTION

Acute coronary syndrome (ACS) was one etiology of atrioventricular (AV) conduction disorders or AV block. This blockage can manifest from first degree to total AV block (TAVB). The previous study reported that 1.9% of all ACS patients presented with TAVB.[1-3] Total occlusion in ST-elevation myocardial infarction (STEMI) was the most common acute coronary

*corresponding author: susantimaretaanggraeni@gmail.com

event to be reported as the cause of AV block. Nevertheless, non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) also cause AV block in several cases. Hemodynamic profile was often deteriorated due to TAVB and thus required timely recognition and treatment.[4]

CASE

A 58 y.o. man came to the emergency department with the chief complaint of heartburn 2 hr before admission to the hospital. Other accompanying symptoms were dizziness, nausea, vomiting, and diaphoresis. Five days earlier, the patient came to the emergency department with a complaint of epigastric pain and nausea. There was no ECG recorded. He was diagnosed with dyspepsia and treated as an outpatient. The risk factors identified were type-2 diabetes mellitus (T2DM) without routine treatment and smoking for 30 yr.

There were indicators of hypoperfusion on the initial observation. The blood pressure (BP) was 60/40 mmHg, the heart rate was 24 beats per min and the distal extremities were cold. There was no previous medication identified to cause bradycardia. The heart auscultation revealed that S1 and S2 were normal and irregular without murmurs or gallops. Lung examination showed vesicular on both lungs, no rales or wheezing were found.

The electrocardiogram (ECG) showed a TAVB pattern with ST-segment depression in leads V4-V6 (FIGURE 1). Two times, 1 mg of atropine sulphate was administered, but there was no improvement in the rhythms. The fluid challenge of 250 mL crystalloid solution was then conducted after signs of congestion were excluded by lung auscultation. After the first fluid challenge, the BP was slightly increased (70/40 mmHg), and then the second fluid challenge was given.

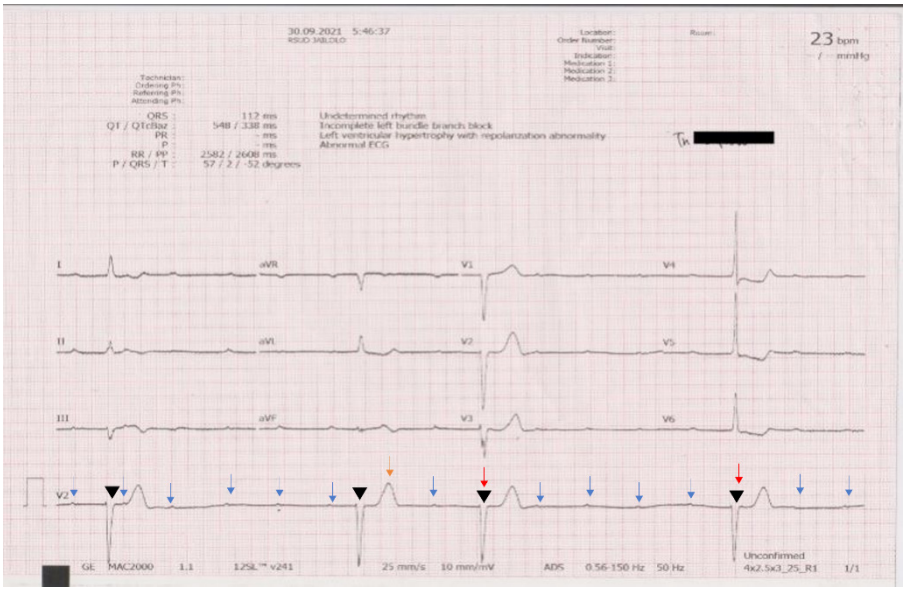

FIGURE 1. Initial ECG at Emergency Department presented total AV block with junctional escape rhythm. Blue arrow: visible P wave; orange arrow: possible P wave buried in T wave; red arrow: possible P wave buried in QRS wave; black arrowhead: narrow QRS wave as junctional escape wave.

TABLE 1. Laboratory work up at the Emergency Department

Laboratory parameters	Flag	Results	Normal value
Haemoglobin (g/dL)	L	13.0	14.0-18.0
Haematocrit (%)	L	38.2	42-54
Erythrocyte (/mm^3)	L	4.33 x 10^6	4.5-6.5 x 10^6
Thrombocyte (/mm^3)	N	230 x 10^3	150-450 x 10^3
Leucocyte (/mm^3)	N	9.4 x 10^3	4.5-11.0 x 10^3
Neutrophile (%)	L	34	54-62
Lymphocyte (%_	H	56.8	25-33
Random plasma glucose (mg/dL)	H	345	<200
Troponin I (ICU) (ng/mL)	H	4.51	<1

Laboratory data (TABLE 1) revealed high random blood glucose (345 mg/dL) and elevated troponin I levels (4.51 ng/mL). The troponin could not be measured at the time of admission due to technical obstacles in our hospital. Due to the reagent's limitations, a serial troponin level measurement could not be achieved. The electrolyte levels of Na and K were within the normal limit. He was assessed for cardiogenic shock due to TAVB, TAVB due to a very high-risk NSTEMI, uncontrolled T2DM, and acute kidney injury (AKI) with a differential diagnosis of chronic kidney disease (CKD). Considering the fact of high-grade AV block with signs of hypoperfusion, it was decided to give epinephrine at 0.1 µg/kg/min, titrated to achieve hemodynamic stability.

The patient met the criteria for pacemaker implantation and immediate percutaneous coronary intervention (PCI), but since there was no catheterization laboratory in our province, only conservative treatment was given to the patient. Medications given during hospitalization were epinephrine, heparin, dual anti-platelet therapy (DAPT), statin, and other symptomatic treatments. Unfractionated heparin (UFH) was used with loading dose 60 unit/kg followed by maintenance dose 12 unit/kg/hr for 5 d. Anti-platelet therapy monitoring was not available in our setting, so we monitor the adverse effect of UFH use, such as bleeding (melena, epistaxis), purpura due to heparin-induced thrombocytopenia (HIT), and anaphylactic reaction of UFH. The use of DAPT consists of a loading dose of 320 mg aspirin and 300 mg clopidogrel at admission, followed by the DAPT daily dose of 80 mg aspirin and 75 mg clopidogrel. We used high dose atorvastatin (40 mg) at admission, followed by a daily dose of 20 mg.

The patient was transferred to the intensive care unit (ICU) for further treatment. Echocardiography revealed normal left ventricle (LV) function with an ejection fraction (EF) of 53%, grade I diastolic dysfunction, LV dilatation with eccentric LV hypertrophy (RWT 0.33), regional wall motion abnormality (RWMA) with infero-septal hypokinetic, normal RV contractility (TAPSE 2.1 cm), and mild mitral regurgitation (E/A < 1). The electrocardiogram was converted to first-degree AV block on day 3 of hospitalization (FIGURE 2A). Epinephrine was subsequently down-titrated until it was finally stopped on day 5 of hospitalization, then he was transferred to the regular ward. On day 8 patient was discharged, and ECG showed sinus rhythm with first-degree AV block (FIGURE 2B).

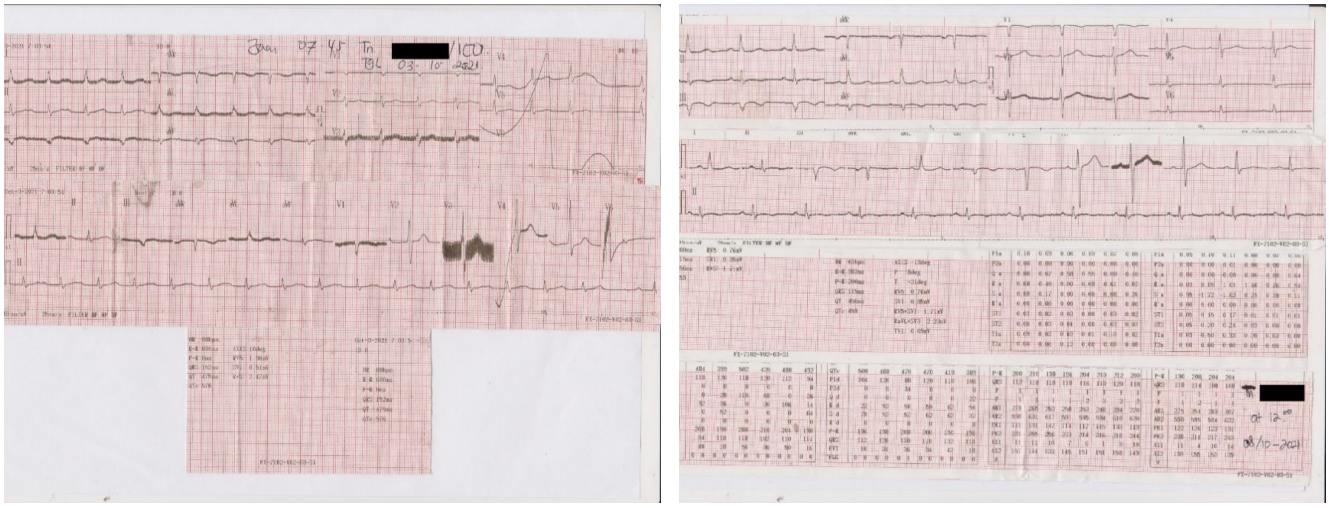

FIGURE 2. A) ECG on day 3 of admission; B) ECG on day 8 of admission

DISCUSSION

The case of TAVB in NSTEMI is not commonly found.[4,5] The AV node was supplied by the right coronary artery (RCA) in 90% of patients (AV nodal branch); and by the left circumflex artery (LCx) in 10% of patients. Therefore, inadequate RCA blood flow would disrupt the conduction system. Two mechanisms that are hypothesized to induce AV block in NSTEMI are vagal and ischemic theories. Vagal theory is established from Bezold-Jarisch reflex. Unmyelinated C-fiber afferent receptors originating from the inferior and posterior walls are sensitive to mechanical and chemical stimuli. Chemical substances such as prostaglandin, serotonin, and free radicals are released from the infarct area, causing parasympathetic activity (hypotension and bradyarrhythmia).[6,7] The second hypothesis is the ischemia theory. The AV node is commonly vascularized by RCA or LCx in the predominance of the left coronary artery. Meanwhile, the bundle of His and conducting fibers is then supplied by the left anterior descending artery (LAD) septal perforators and either RCA or LCx. Inadequate vascularization due to partial or total occlusion leads to disruption of the conduction system. Conduction disorders were commonly found in inferior MI due to RCA occlusion.[8,9]

Based on the 2020 ESC Guideline for the management of ACS in patients presenting without persistent ST-segment elevation, our patient was classified as a very high-risk NSTEMI due to the presence of cardiogenic shock and life-threatening arrhythmia. Therefore, an immediate invasive strategy should be conducted to manage our patient. Due to inadequate resources and no catheterization laboratory facilities in our area, this revascularization strategy was unfeasible. In TAVB with reversible causes, treating the etiology would resolve the conduction abnormality, as in thyroid disorders, Lyme disease, cardiac sarcoidosis, viral myocarditis, and intoxication of some heart medications.[10] Apart from those etiologies, Acute coronary syndrome has been reported as a reversible cause of TAVB.[11-13]

Conservative management was then conducted by our team. Initial DAPT and anticoagulants were administered to our patient based on standard medical therapy of ACS. Meanwhile, the management of TAVB was based on the 2018 ACC/AHA/HRS guideline. Bradycardia due to AV block with hemodynamic compromise is managed by removal of potential causative factors

concomitant with medical therapy. Second or third grade AV block should be managed by atropine administration to increase ventricular rate, improve AV conduction, and relieve symptoms. Aminophylline can be considered to be added if the etiology of AV block is acute inferior MI. Meanwhile AV block due to other causes can be managed by β-adrenergic agonists such as isoproterenol, dopamine, dobutamine, or epinephrine. Cardiac pacing is recommended if the AV block do not respond to medical therapy.

Epinephrine was chosen to improve the hemodynamic status in this case. Other β-adrenergic agonists may also be used, but in our setting, only epinephrine was available. Epinephrine acts on α- and β-adrenergic receptors. In high doses, epinephrine exerts action on α-1 receptors, increasing heart rate and myocardial contractility.[14] Epinephrine is also preferred in a patient with a hypotensive state.[15] Hemodynamic improvement was achieved by our patient after up-titrating the epinephrine dose with close monitoring. In this case, the ECG was converted into a first-degree AV block. It was suggested that restoration of perfusion in the setting of acute MI leads to improved conduction.

Symptomatic bradycardia in TAVB and NSTEMI should be managed altogether. In cases of myocardial ischemia, adequate reperfusion will improve electrical conduction. Implantation of cardiac pacing in acute MI is considered based on clinical presentation to avoid unnecessary pacemaker implantation. Implementation of the guideline as a standard of therapy should be accompanied by the availability of standard pharmacologic agents as well as the presence of cardiology specialists in every hospital in Indonesia. As an archipelago country, Indonesia has a lot of obstacles to equalizing health services, either in urban or rural areas. Therefore, government should arrange policies to reduce the gap of inequalities in health services.

CONCLUSION

Standard medical treatment for TAVB with NSTEMI is reperfusion, followed by cardiac pacing as necessary. Due to lack of access to catheterization laboratory, conservative management based on both atrioventricular block and the NSTEMI guideline are conducted. In this case, antithrombotic agents and β-adrenergic agonists together improve cardiac conduction and hemodynamic status. In the setting of limited cardiovascular care, those antithrombotic agents and β-adrenergic agonists can be considered to manage TAVB with NSTEMI with close monitoring.

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