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Editorial

Pandemi Covid-19 tetap menjadi topik menarik untuk dibahas dan dicermati. Dalam edaran World Health Organization (WHO), dinyatakan bahwa kondisi post Covid-19 masih berpotensi memberikan pengaruh pada manusia pada segala usia, meski yang memiliki gejala ringan pada saat terinfeksi. Bahkan WHO menyatakan bahwa risiko tersebut lebih tinggi pada orang-orang yang pernah mengalami infeksi berat Covid-19. Itu sebabnya, penelitian terhadap kelanjutan infeksi virus ini masih mendapat perhatian besar dan membuka peluang dalam memperoleh data serta melakukan penyelidikan lebih lanjut.

Terlebih setelah pandemi dinyatakan sebagai endemi, kesempatan untuk kembali meneliti semakin menggeliat. Banyak penelitian yang memberikan informasi baik berupa tinjauan klinik, laboratoris, maupun biologi molekuler, dan diwujudkan dalam artikel yang baik. Hal ini menunjukkan bahwa pengembangan ilmu maju dengan sangat pesat, termasuk di Indonesia.

Pada dasarnya, penelitian adalah jawaban atas suatu proses pendidikan, wujud suatu pengembangan intelektual dan proses berpikir yang logis dan sistematis. Setelah dijejali oleh teori dan praktek, seorang peserta didik harus mampu mengembangkan pertanyaan yang dilandasi latar belakang yang jelas. Pada gilirannya nanti, pertanyaan itu harus bisa dijawab dengan berdasar data yang valid, sehingga luaran yang dihasilkan adalah sebuah hal yang bermanfaat dan dapat diterapkan pada kondisi yang sesuai.

Pada edisi ini, terdapat artikel-artikel yang sarat dengan ilmu. Dengan kaidah penelitian yang baik, dihasilkan tulisan yang berkualitas. Harapan selanjutnya adalah muncul peneliti-peneliti yang tekun dan penuh semangat berjuang untuk mengembangkan ilmu, dan tanpa ragu berbagi ilmu melalui artikel ilmiah sebagai bagian dari pengabdian dalam dunia kesehatan.

Selamat meneliti dan berbagi ilmu.

Editor

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Original Article

Risk Factors for Mortality Among Confirmed Covid-19 Patients at RSUP Dr. Kariadi

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Abstract

Background : Coronavirus Disease 2019 (COVID-19) is a communicable disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11, 2020 the World Health Organization (WHO) declared COVID-19 as pandemic causing mortality in more than 150 countries. China reports the most case is among people aged 30–79 years old and male, meanwhile in Italia the most case is among patients with cardiovascular disease, diabetes, chronic diseases, hypertension, and cancer. This encourages researcher to examine risk factors causing mortality among patients with confirmed COVID-19.
Methods : This is an observational study with multivariate analytical test. The samples involved medical records of died patients with confirmed COVID-19 at RSUP Dr. Kariadi. Risk factors being studied involved age, gender and comorbidities such as hypertension, diabetes, pneumonia, chronic obstructive pulmonary disease (COPD), heart disease, kidney disease, and cancer. Data were analyzed using multiple logistic regression with univariate, bivariate, multivariate, confounding and interaction tests.
Results : An increased risk for mortality was found among confirmed COVID-19 patients aged over 60 years (3.25 times), suffered from hypertension (2.09 times), pneumonia (4.77 times), cancer (11.89 times), heart disease (3.55 times), and kidney disease (5.23 times).
Conclusion : Risk factors involving age, hypertension, pneumonia, cancer, heart disease, and kidney disease increase risk for mortality among patients with confirmed COVID-19. The risk is heightened as patients aged older than 60 years old suffering from pneumonia and cancer simultaneously.

Keywords : Risk factor, Confirmed COVID-19, Mortality

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a communicable disease caused by *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2).[1] On March 11, 2020 the WHO declared COVID-19 as pandemic with increasing number of cases causing death in more than 150 countries.[2,3] Indonesia reported first case of COVID-19 on March 2, 2020 and patient number kept growing.[2] On July 9, 2020 the Ministry of Health reported 70.738 confirmed cases of COVID-19 and 3.417 deaths (Case Fatality Rate/CFR 4.8%) spreading over 34 provinces.[2,3] The COVID-19 task force on February 20, 2021 reported a total of 1.271.353 confirmed cases and 34.316 death rate or 2.7% of the confirmed cases in Indonesia. Central Java was in the third most confirmed cases in Indonesia.[4] The Tanggap COVID-19 of Central Java reported that of 148.819 confirmed cases, 9.306 patients were died.[5] The Siaga Corona of Semarang City reported 30.333 confirmed cases and 2.374 deaths consisting of 1.651 residents of Semarang and 723 non-residents.[6] The Chinese Center of Disease Control (CDC) declared the most case was among people aged 30–79 years old and male, while in Italia the most case was among patients with comorbidities such as heart disease, diabetes, chronic disease, hypertension, and cancer.[7,8]

The death of patients with confirmed COVID-19 was influenced by some risk factors. The association between risk factors and mortality is stronger among older people. People aged over 75 years without additional risk factor have equal risk of those younger than 65 years old.[9] Male has three times higher risk for mortality compared with female.[10,11] Hypertension is the most common comorbidity of COVID-19 with death rate of 58.3%. The second most common comorbidity is diabetes with death rate of 49%. Diabetes and hypertension damage blood vessel structure worsening condition during infections.[12,13] Pneumonia has high fatality rate as lung injury results in lower resistance against viruses and may lead to ARDS.[13] Some studies show that people suffering from COPD have a risk of 1.38 times being infected by COVID-19 compared with those without this condition.[14,15] Respiratory symptoms is the main manifestation of COVID-19, but growing evidences show that it also attacks heart. It was reported that 16.7% and 7.2% COVID-19 patients experience arrhythmia and acute myocardial infarction respectively.[12,13,16] Severe kidney diseases have a great mortality risk, even greater than other comorbidities.[17,18] Since the emergence of COVID-19, cancer patients have a greater risk of being infected and died.[19] For that reason, this study was conducted to examine risk factors such as age, gender, and other comorbidities such as hypertension, diabetes, pneumonia, COPD, heart disease, kidney disease, and cancer which may increase risk for mortality among patients with confirmed cases.

METHODS

This is an observational study with multivariate analytic test. This study recruited samples of medical records of patients died of confirmed COVID-19 having risk factors involving age, gender and comorbidities such as hypertension, diabetes, pneumonia, COPD, heart disease, kidney disease, and cancer at Emergency Room, isolation room and isolation ICU of RSUP Dr. Kariadi. This study excluded patients with probable and suspected COVID-19. Samples were recruited through consecutive sampling. At least 57 medical records meeting inclusion criteria were recruited. The age of medical records was 10 months between March and December 2020.

The data were analyzed with multivariate logistic regression using Excel 2019 and SPSS version 26. Univariate analysis was to describe each independent variable. A bivariate variable selection was conducted between each dependent and independent variable. Once these variables were found to be significant, they were included in the further analysis involving multivariate, confounding, and interaction tests.

This study got ethical approval from research ethic committee of Diponegoro University No.104/EC/KEPK/FK-UNDIP/IV/2021.

RESULTS

This study commenced on May to July 2021 by recruiting samples at Medical Record Department of RSUP Dr. Kariadi. Research samples were recruited consecutively to gather all data within specified period. The secondary data gathered were confirmed cases at RSUP Dr. Kariadi between March and December 2020. There were 184 data meeting inclusion criteria used in the multivariate analysis model encompassing univariate, bivariate, and multivariate analysis.

Data analysis shows 184 confirmed cases involving 95 patients survived (51,6%) and 89 patients died (48,4%) (Table 1).

Risk factors of patients died consist of male 53 patients (49,5%), age over 60 years 32 patients (69,6%), hypertension 38 patients (60,3%), diabetes 28 patients (52,8%), pneumonia 42 patients (73,7%), cancer 10 patients (90,9%), heart disease 12 patients (75%), kidney disease 8 patients (80%), and COPD 2 patients (100%).

Bivariate analysis shows no significant relationship between death risk among patients with confirmed COVID-19 and risk factors including male, diabetes, and COPD so these risk factors do not affect death rate. However, there is a significant association between death rate and risk factors consisting of age over 60 years, hypertension, pneumonia, cancer, heart disease, and kidney disease. Thus, having one or more of these

TABLE 1
Confirmed COVID-19 Patients

Variable	Frequency	%
Death		
Yes	89	48.4
No	95	51.6
Patients died with risk factors		
Male	53	49.5
Age (>60)	32	69.6
Hypertension	38	60.3
Diabetes	28	52.8
Pneumonia	42	73.7
Cancer	10	90.9
Heart disease	12	75
Kidney disease	9	81.8
COPD	2	100

Note: Chi Square Analysis. Significance of p<0.5.

TABLE 2
Bivariat Analysis

Variable	OR (95% CI)	p
Male	1.12 (0.62–2.01)	0.710
Age (>60)	3.25 (1.60–6.63)	0.001
Hipertension	2.09 (1.12–3.90)	0.020
Diabetes	1.28 (0.68–2.43)	0.442
Pneumonia	4.77 (2.39–9.51)	0.000
Cancer	11.89 (1.49–94.98)	0.019
Heart disease	3.55 (1.01–11.44)	0.034
Kidney disease	5.23 (1.09–24.92)	0.038
COPD	$17.64x10^{-11}$ (0)	0.999

Note: Chi Square Analysis. Significance of p<0.5.

risk factors increase death risk among those with confirmed COVID-19. The death risk of patients with confirmed COVID-19 aged over 60 years, and suffered from hypertension, pneumonia, cancer, heart disease and kidney disease increases 3.25, 2.09, 4.77, 11.89, 3.55, and 5.23 times respectively in comparison with confirmed COVID-19 patients survived.

In the multivariate analysis, variables included in the model involved age, hypertension pneumonia, cancer, heart disease, and kidney disease. This model selected risk factors owned by patients with confirmed COVID-19 increasing death risk. The end results show that age, pneumonia, and cancer owned by patients with confirmed COVID-19 simultaneously increase death risk. The confounding test shows that cancer acts as a confounding variable in which cancer risk factor affect death rate among patients with confirmed COVID-19. The interaction test found an interplay between risk factors of pneumonia and age in which death risk increase as they are owned simultaneously.

DISCUSSION

1. General descriptions and increased death risk

The variable of male does not increase death risk different from other study stating that male has greater risk compared with female.[15,20,21] Patients aged over 60 years have a heightened death risk of 3.25 times compared with those aged below 60 years.[20,22] The averaged age of confirmed COVID-19 patients died at RSUP Dr. Kariadi is 57 years. The youngest patient aged 21 years while the oldest patient aged 77 years.

The variable of hypertension increases death risk 2.09 times among confirmed COVID-19 patients. Hypertension commonly experienced by confirmed COVID-19 patients died is type II hypertension. Some patients were suffering from type I hypertension and controlled hypertension but significantly lower than type II hypertension. The variable of diabetes does not increase death risk among patients with confirmed COVID-19 in contrast with previous studies.[13,17,23] The confirmed cases at RSUP Dr. Kariadi were dominated by type II diabetes followed by diabetic ulcer.

The patients with confirmed COVID-19 suffering from pneumonia during clinical investigations have an increased death risk of 4.77 times.[15] The confirmed COVID-19 patients with cancer have a greater death risk of 11,89 time in comparison with those without cancer.[24] Some patients with confirmed COVID-19 died at RSUP Dr. Kariadi suffers from some types of cancer involving *nasofaringeal cancer (malignant neoplasm of nasopharynx), non hodgkin lymphoma (tonsil LNH), medulla spinalis tumour (Multiple Myeloma),* tumor in frontal region, *ovarian cancer, breast cancer*, and *invacive ducral carcinoma*.

The death risk among confirmed COVID-19 patients suffering from heart disease increases 3.55 times.[25,26] The heart disease experienced by confirmed COVID-19 patients died at RSUP Dr. Kariadi involves *congestive heart failure* (CHF), STEMI (ST *elevation myocardial infarction*), NSTEMI (non-ST *elevation myocardial infarction*), *coronary artery disease* (CAD), and *supraventricular tachycardia* (SVT). The death risk of patients with confirmed COVID-19 suffering from kidney disease increases 5.23 times.[27] Types of kidney

disease among confirmed COVID-19 patients include *chronic kidney disease* (CKD), *acute kidney injury* (AKI) and azotemia. Some CKD patients underwent dialysis therapy. No increased death risk was found among those with confirmed COVID-19 and COPD.[28,29] The type of COPD experienced by confirmed COVID-19 patients is emphysema.

2. The association between risk factors and mortality

RSUP Dr. Kariadi is a referral hospital for COVID-19 providing care to 727 confirmed cases in 2020. Of the many cases, the percentage of male patients died was 49.5% lower than that of female patients. This finding is in accordance with a study conducted by Dehingia N showing that the percentage of female patients died was higher than that of male patients which occurred in India, Vietnam, Nepal and Slovenia.[30] However, a study conducted by Jim JM, *et al.* shows different findings as generally male has higher risk related to biological and habitual factors than female does.[21] The biological factors involve immune response and habit such as smoking. These differences may occur as a result of incomplete data, geography, biased data identification, or countries with high risk of women's health issues.[21]

Patients aged above 60 years have a high death rate of 69,6%. This finding is in line with a study conducted by Indarwati R stating that this may be caused by factors such as comorbidity or lowered immune system. Psychological factors also play an important role as limitation of social interaction lowers mental health.[22] The limitation of social interaction experienced by elderly involves limitation of participation in Posyandu Lansia. Posyandu lansia is a place where elderly gathers with peers so they do not feel lonely.[22]

There is an association between COVID-19 and hypertension worsening patient's conditions. During this study, 60.3% patients died was found to have hypertension. This finding is corroborated by a study by Du Y, *et al.* stating that SARS-CoV-2 viruses possess ACE 2 receptors. Anti-hypertensive drugs acting as ACE inhibitor increase the number of ACE 2 receptors on cell surface. For that reason, patients consuming anti-hypertensive drugs experience more severe infection which may lead to death.[31] In addition, a study by Yustinawati R and Achadi explains that death may occurs as level of ACE 2 drastically drop even before immune systems are able to control virus population.[20]

A meta-analysis by Corona G, *et al.* indicates that COVID-19 patients suffering from diabetes possess death risk twice higher than those without diabetes. There is no specified explanation related to the causes of this elevated mortality, but some factors may be responsible such as lung dysfunction related to decreased lung volume, lung diffusion capacity, ventilation control, and bronchomotor tone. Prognosis may be compromised as patients suffer from hyperglycemia. Besides, diabetic patients are more susceptible for infections.[32] However, this study contradicts these findings as patients suffering from confirmed COVID-19 and diabetes simultaneously died at RSUP Dr. Kariadi (52.8%) do not have an increased death risk.

A high number of patients with confirmed case and pneumonia died at RSUP Dr. Kariadi (73.7%). This finding is in line with a study conducted by Hidayani WR explaining that mortality may be caused by symptoms such as fever, tachypnea (≥ 30x/minutes), dyspnea, and low saturated oxygen.[15] Another study conducted by Elezkurtaj, *et al*. elucidates that purulent pneumonia with and without abscess found on died patients during an autopsy was most numerous in comparison with other risk factors being studied.[26]

A study conducted in Norway by Johannesen TB, *et al.* comparing cancer and non-cancer patients found no significant increase of death risk of confirmed COVID-19 patients suffering from overall cancer, but an increased death risk was found among those suffering from metastatic cancer.[24] In other hand, the death rate of cancer patients at RSUP Dr. Kariadi was 90,9% which is in line with a study conducted in China by Zhou Y, *et al*. in which the death rate of confirmed COVID-19 patients was 11.7% higher than those without cancer. The most commonly cancer is lung cancer followed by breast cancer and rectal cancer.[33]

In this study, the death rate of patients suffering from heart disease was 75%. This finding is in accordance with previous study by Harrison SL and Cordero A, *et al.* claiming that there was an increase of death rate of confirmed COVID-19 patients suffering from heart disease. It was caused by pro-inflammatory response related to upper respiratory tract infection, immune dysregulation worsening susceptibility and severity, smoking and obesity among heart disease patients.[23,34]

The patients with confirmed COVID-19 suffering from kidney disease died at RSUP Dr. Kariadi was 80%. A study conducted by Drew C, *et al.* explained that COVID-19 impairs cell membrane permeability through inflammatory cytokine and antigen-antibody complex formation.[35] A study conducted in Italia by Gibertoni D, *et al.* found that majority of confirmed COVID-19 patients suffering from kidney disease is old and had multiple comorbidities. The death rate of patients suffering from kidney disease are higher than those without kidney disease as this condition had chronically affected kidney.[27]

A study conducted by Lee SC, *et al*. found that COPD worsens clinical outcomes as poor lung function. COPD is a heterogenous disease with various severity levels, exacerbation frequency, and comorbidities.[29] Gerayeli FV, *et al*. claimed that confirmed COVID-19 patients suffering from COPD owned a high death risk which may be caused by an increased ACE 2 receptors in

respiratory tract and lung. COPD is also tightly related to impaired immune sistem.[28] In comparison with previous two researches, this study did not find an increase of death risk.

3. Research limitations

This study has limitations. The medical records being analyzed was only 184 of 727 as some medical records could not be found, data was mixed with other variables, and incomplete data. Besides, the proposed period of study was between March and December, however the diagnose of confirmed COVID-19 was adopted since July so the study period was altered.

There is inaccuracy in processing data which may lead to bias. The definition of heart disease, kidney disease, and COPD had not been specified so it had broad meaning. Other risk factors found during study did not included as risk factors.

CONCLUSION

The conclusions of this study are some risk factors involving age, hypertension, pneumonia, cancer, heart disease, and kidney disease increase death risk among patients with COVID-19 patients. Patients aged over 60 years suffering from pneumonia and cancer simultaneously possess higher death risk. Gender, diabetes and COPD do not increase death risk.

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Original Article

The Relationship between Pre-Operative Clinical Characteristics with Changes in Post-Operative Memory Scores on Temporal Lobe Epilepsy Patient

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Abstract

Background : Most temporal lobe epilepsy (TLE) will become seizure-free after anterior temporal lobectomy (ATL) surgery but often result in cognitive decline, specifically in verbal or visual memory. This study examined the relationship between several demographic characteristics and pre-operative clinical conditions with changes in pre-post surgical memory of TLE patients.
Methods : This study used a retrospective cohort in which the subjects were TLE patients who had undergone ATL surgery at Kariadi Hospital or Telogorejo Hospital, Semarang. Demographic variables include the age of onset, duration of illness, level of education, and clinical variables include seizure frequency, EEG waveform, number of AED, lesion site, and IQ score.
Results : Memory re-examination was conducted on TLE patients who had undergone surgery between 2018 and 2021, with 55 subjects who fulfilled the criteria. Characteristics of the subjects were male 31(56%) males, 38% Senior High School education, the mean age of onset was 13.87±6.899, age at surgery was 27.67±9.802, 21 (39%) normal pres-surgical EEG waveform, 31 (56%) lesion on the left and the most frequent seizures occurred in 36 subjects (65%). Statistical test results showed a significant relationship between age of onset and changes in verbal memory recognition scores (p 0.044), lesion side with changes in verbal memory task scores (p 0.018), recall (p 0.005), recognition (0.008), and IQ scores with changes in visual memory construction recall (p 0.041)
Conclusion : Age of onset, lesion side, and IQ score characteristics were related to the changes in memory scores between pre- and post-operative anterior temporal lobectomy in TLE patients.

Keywords : temporal lobe epilepsy, post-operative memory changes, anterior temporal lobectomy

INTRODUCTION

Epilepsy is one of the severe brain disorders afflicting more than 70 million people worldwide.[1] It has become one of the world's health priorities because of the necessity of providing relatively expensive drugs to reduce morbidity, disability, and mortality.[2] It can also have unwanted effects on mental development, cognition, and behavior, as well as decreased intelligence and memory problems.[3] Epilepsy is classified as a seizure,[4] and an estimated 60% manifest as focal seizures.[5] Focal epilepsy patients experience ongoing seizures, are resistant to drugs[6] and site-specific cognitive impairment.[7] Based on localization, temporal lobe epilepsy (TLE) is the most common type of refractory focal epilepsy.[8] Breuer *et al*. found a progressive decline in memory of 20–25% in chronic TLE patients over a 4-year interval. It was associated with lower initial intellectual capacity, duration of epilepsy, seizure frequency, history of status epilepticus, polypharmacy, and progressive hippocampal atrophy.[9]

Mesial temporal lobe epilepsy (MTLE) syndrome with hippocampal sclerosis is one of the epilepsy types with good surgical outcomes.[10] The success rate of post-operative seizure-free is about 60–80% of cases.[11–14] Sallie Baxendale reported that studies analyzing cognitive function (memory) of TLE patients for ≥5 years are rare. Most of those which studied for 1–2 years post-operatively obtained stable results for comparing pre- and post-operative memory function.[15] However, Witt *et al*. analyzed adult MTLE patients with surgery in Germany and found a change in memory between pre- and post-operatively. There was a more significant decrease in verbal task memory and recall on both sides, specifically on the left.[16] Mathon *et al*. also demonstrated that the variable anterior temporal lobectomy (ATL) and hippocampal lesions on the left side worsened post-operative verbal memory outcomes.[17] There are still mixed outcomes regarding the results of pre-operative memory tests compared to post-operative temporal lobe epilepsy patients. Until this day, there has no evidence of research in Indonesia that analize the changed in memory function of post-ATL TLE patients, even though the impact on memory function is very important for the patients and as a consideration in patient care delivery.

Therefore, it is necessary to study the relationship between several individuals and clinical factors with changes in memory before ALT surgery in TLE patients.

OBJECTIVE

This study explored the association between pre-operative demographic and clinical features and memory changes after surgery in Indonesian patients with TLE.

METHODS

This study was conducted using a non-experimental and retrospective cohort design. The samples used were obtained from the human population, namely TLE patients with known epileptic seizures originating from the temporal lobe region of one side. The diagnosis was based on anamnesis, Electroencephalography (EEG), Magnetic resonance imaging (MRI), and Positron emision tomography (PET) scan with normal hippocampus or sclerosis. The examination was carried out within the past 1-4 years when the ATL surgery was programmed. Furthermore, the pre-operative memory scores of the subject were evaluated and compared to post-operative scores.

Inclusion criteria were TLE patients of any gender, aged 8–60 years, who underwent pre-operative and surgical examinations at Kariadi Hospital or Telogorejo Hospital in Semarang. Exclusion criteria included a history of brain or meningeal infection, stroke, dementia, post head injury, and other brain structural abnormalities except for focal cortical dysplasia in the temporal lobe.

The materials and tools used are: (1) Pre-operative ATL medical records in patients with TLE who were operated on for the period 2018–2021, including anamnesis: age of onset, age at surgery, last education, number of antiepileptic drugs, seizure frequency, as well as results of an examination of memory scores, IQ scores, EEG recordings, MRI photo impression, lesion side, and anatomic pathology impression. (2) The results of the pathological examination of the anatomy of the hippocampus are based on the description of gliosis and neuronal loss on cornu ammonis 1,2,3,4 stated by a neuropathologist. (3) Memory scores are expressed in numbers from each sub, namely verbal memory of task, recall, recognition, and visual memory of task construction and recall. The examination was conducted with verbal and visual memory (Neurobehavior examination book : Wordlist task & recognition, Neurorestoration study group of Indonesia Neurology Association, 2010). (4) A psychologist conducted the IQ examination using WAIS protocol for adults (16–65 years old) and WISC for children (8–15 years old), and the IQ score is the total IQ. (5) The patients were examined for verbal and visual memory scores evaluation between 1 and 4 years post-operatively. (6) The results of this post-operative memory score examination analyzed changes in the form of an increase/constant or decreased compared to the memory score before surgery. (7) Anatomical pathology laboratory equipment. (8) Statistical analysis was carried out by computer using SPSS for windows version 26.

Comparative tests were performed using Pearson Chi Square and Fisher's Exact test for nominal data. Data with a 2x2 table if it meets the requirements, the Pearson Chi Square test is carried out, if it does not meet the

requirements (expected count < 5), the Fischer's Exact test is carried out. Data with 2x3 and 2x4 tables were tested by Pearson Chi Square. Comparative test between numeric and nominal two groups of data were performed using independent t test if the data has normal distribution, but if it has abnormal distribution it will carried out with Mann Whitney test after the attempt to normalize data is unuseful. the statistic was significance if p<0,05. (9) The ethical clearance was conducted by the Health Research Ethics Commission of the Undip Medical Faculty Semarang with no 451/EC/FK-RSDK/2020, and Telogorejo Hospital Semarang no 20978/TU.710/KEPK/K/2020. The permit of study was received from Kariadi General hospital no DP.02.01/I.II/3746/2020 and Telogorejo Hospital no 29665/TU.710/DIR/K/2020. (10) Informed consent is carried out at the time of initial contact with prospective research subjects, the purpose and benefits of the research are explained and they are given independence whether to participate or to refuse of becoming research subjects. Each research data in the form of identity, documents and the confidentiality will be guaranteed, namely by not including the identity of the subject, and the data is only used for research, education and science purposes.

RESULTS

This study was conducted on TLE subjects who had surgery between 2018 and 2021. Based on data collection, 71 patients with TLE had unilateral hippocampal sclerosis, and 16 subjects were excluded. This is because the anatomical pathology laboratory data were incomplete, refused to be included in this study, the contact number could not be reached, and the location of residence was far from the local referral hospital. Demographic and clinical characteristics included gender, age of onset, education level, age of surgery, length of illness, interictal epileptic wave, number of AEDs, hippocampal lesion site, and frequency of seizures.

From Table 1, the results showed that the subjects were 55, with a male gender distribution of 31 (56.4%), and the level of education that graduated from High School was 25 (38.2%). The mean age of onset was 13.87±6,899, the mean age at surgery was 27.67±9,802 (8-47), and the average length of illness was 13.8±8.818 years. Meanwhile, the EEG showed interictal epileptic discharges in only 9 (17%) subjects, the mean number of AED drugs taken was 2.32±0.976, 24 (43.6%) had hippocampal sclerosing lesions on the right side, 36 (65.5%) had frequent seizures, and the mean total IQ and median score were 87,91 ±16,224 and 92.

In general there are several postoperative memory examinations that show improvement or the same results as in visual construction, visual contraction recall and verbal recognition. However, there are memory examination that have decreased, such as verbal memory recall as shown in Table 2.

Bivariate analysis of the relationship between clinical variables and changes in verbal task memory scores at Table 3 shows that the results of postoperative memory examination have significant in lesion side with RR 1.830 (p=0.018).

The relationship between clinical variables and changes in verbal recall memory scores in bivariate analysis at Table 4 shows that the results of postoperative memory examination have significant in lesion side with RR 2.296 (p=0.005) .

The relationship between clinical variables and changes in verbal recognition memory scores in bivariate analysis of at Table 5 shows that the results of postoperative memory examination have significant in age of onset (p=0.044) and lesion side with RR 1.722 (p=0.008).

Bivariate analysis of the relationship between clinical variables and changes in visual construction recall memory scores at Table 6 shows that the results of postoperative memory examination have significant in

TABLE 1
Demographic and Clinical Characteristics of Pre-operative Subjects (n=55)

Characteristics	Limit	Frequency (%)	Mean ±SD (Min–Max)	Median (Min–Max)
Gender	Male	31 (56.4%)		
	Female	24 (43.6%)		
Education	Special School	2 (3.6%)		
	Elementary School	6 (10.9%)		
	Junior High School	1 (1.8%)		
	Senior High School	25 (38.2%)		
	College	21 (25.5%)		

TABLE 1. Continued.

Characteristics	Limit	Frequency (%)	Mean ±SD (Min–Max)	Median (Min–Max)
Age of onset	Year		13.87 ± 6.899	13.00
Operated age	Year		27.67 ± 9.802	25.00
Ill duration	Year		13.8 ± 8.818	12.00
Seizure frequency	Often (>3x per month)	36 (65.5%)		
	Moderate (1-2x per month)	15 (27.3%)		
	Infrequent (<1x per month)	4 (7.3%)		
Number of AED	Tablet per day		2.32 ± 0.976	2.00
Interictal EEG wave	- Normal	21 (39.6%)		
	- Slow general/focal	9 (15.1%)		
	- Ipsilateral focal epilepsy	10 (17%)		
	- Epilept bilatr/general ± slow	15 (28.3%)		
Lesion side	Right	24 (43.6%)		
	Left	31 (56.4%)		
IQ Score	Number		87.91 ± 16.224	92

AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 2
Changes in Pre- and Post-operative Memory Score

Memory Type	Pre-operative	Post-operative	Score Change	
			Increase/keep	Decrease
Verbal *Task*	19.00 ± 4.944	18.16 ± 5.776	29 (52.7%)	26 (47.3%)
Verbal *Recall*	6.27 ± 2.181	5.15 ± 2.415	25 (45.5%)	30 (54.5%)
Verbal *Recognition*	9.10 ± 1.222	8.85 ± 1.495	35 (63.6%)	20 (36.4%)
Construction Visual	9.42 ± 2.455	10.31 ± 1.574	52 (94.5%)	3 (5.5%)
Visual Construction Recall	8.22 ± 3.083	8.71 ± 3.154	47 (85.5%)	8 (14.5%)

IQ score (p=0.041).

DISCUSSION

The results obtained a significant relationship between the hippocampal lesion side and verbal memory scores consisting of task, recall, and recognition changes. However, there was no significant relationship between the lesion side and changes in visual memory scores. This finding is consistent with previous studies showing that lesions on the left side adversely affected verbal memory both pre- and post-operatively.

In epilepsy patients, memory deficits result from disrupted normal cognitive networks by epileptic activity. The left hemisphere also plays a vital role in reorganizing verbal and non-verbal memory. Therefore, TLE in the left hemisphere indicates more severe memory impairment. Allone *et al*. showed that in the pre-operative condition, the dominant verbal disorder was the most common form in both the left (65.9%) and right (48.8%) sclerosis groups. The verbal memory index was lower than the visual, specifically in patients with left sclerosis. In the post-operative condition, improvement in memory index was found in 23.3–36.6% of patients. Memory improvement was similar between left and right hippocampal sclerosis, as well as verbal and visual domains.[13] Hypocampectomy can improve memory index regardless of the surgical site or the domain of

TABLE 3
Bivariate Analysis on the Relationship of Clinical Variables with Changes in Verbal Task Memory Score

Variable		Verbal Task Memory Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	13.28 ± 6.06	14.54 ± 7.80	0.55€	
	Median	12 (5–36)	13 (1–33)		
Ill duration	Mean	14.34 ± 8.06	13.19 ± 9.72	0.35€	
	Median	13 (3–33)	10 (3–34)		
Seizure Frequency	Often	22 (61.1%)	14 (38.9%)	0.19*	
	Moderate	5 (33.3%)	10 (66.7%)		
	Infrequent	2 (50%)	2 (50%)		
Education level	Special School	2 (100%)	0 (0%)	0.29*	
	Elementary School	2 (33.3%)	4 (66.7%)		
	Junior High School	1 (100%)	0 (0%)		
	Senior High School	15 (60%)	10 (40%)		
	College	9 (42.9%)	12 (21.8%)		
Interictal EEG Wave	Normal	12 (57.1%)	9 (42.9%)	0.89*	
	Slow general/focal	5 (62.5%)	3 (37.5%)		
	Ipsilateral focal epilepsy	4 (44.4%)	5 (55.6%)		
	Bilateral/generalized	8 (53.3%)	7 (46.7%)		
	Epilepsy/± slow wave				
Number of AED	Mean	2.38 ± 1.08	2.25 ± 0.85	0.81€	
	Median	2 (1-5)	2 (1–5)		
Lesion Side	Right	17 (70.8%)	7 (29.2%)	0.018$	1.830 (1.097–3.053)
	Left	12 (38.7%)	19 (61.3%)		
IQ score	Mean	86.72 ± 17.57	89.23 ± 14.81	0.57&	
	Median	93 (47–108)	91.5 (54–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test
AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 4
Bivariate Analysis on the Relationship of Clinical Variables with Changes in Verbal Task Memory Score

Variable		Verbal Recall Memory Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	13.44 ± 6.97	14.23 ± 6.94	0.81€	
	Median	13 (1–36)	12 (5–33)		
Ill duration	Mean	11.92 ± 5.74	15.37 ± 10.58	0.48€	
	Median	12 (3–25)	11 (4–34)		

TABLE 4. Continued

Variable		Verbal Recall Memory Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Seizure Frequency	Often	17 (47.2%)	19 (52.8%)	0,69*	
	Moderate	7 (46.7%)	8 (53.3%)		
	Infrequent	1 (25%)	3 (75%)		
Education level	Special School	0 (0%)	2 (100%)	0.29*	
	Elementary School	3 (50%)	3 (50%)		
	Junior High School	0 (0%)	1 (100%)		
	Senior High School	10 (40%)	15 (60%)		
	College	12 (57.1%)	9 (42.9%)		
Interictal EEG Wave	Normal	13 (61.9%)	8 (38.1%)	0.35*	
	Slow general/focal	3 (37.5%)	5 (62.5%)		
	Ipsilateral focal epilepsy	4 (44.4%)	5 (55.6%)		
	Bilateral/generalized	5 (33.3%)	10 (66.7%)		
	Epilepsy/± slow wave				
Number of AED	Mean	2.26 ± 0.92	2.37 ± 1.03	0.68€	
	Median	2 (1–5)	2 (1–5)		
Lesion Side	Right	16 (66.7%)	8 (33.3%)	0.018$	2.296 (1.23–4.26)
	Left	9 (29%)	22 (71%)		
IQ score	Mean	88.04 ± 15.50	87.80 ± 17.07	0.96&	
	Median	93 (47–108)	91 (47–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test
AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 5
Bivariate Analysis on the Relationship of Demographic and Clinical Variables with Verbal Recognition Memory Score Changes

Variable		Verbal Recognition Memory Score Changes			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	15.37 ± 7.35	11.25 ± 5.21	0.044€	
	Median	14 (5–36)	10.50 (1–22)		
Ill duration	Mean	13.49 ± 8.32	14.35 ± 9.83	0.92€	
	Median	12 (3–34)	12 (3–33)		
Seizure Frequency	Often	25 (69.4%)	30.6 (20%)	0.46*	
	Moderate	8 (53.3%)	46.7 (12.7%)		
	Infrequent	2 (50%)	50 (3.6%)		
Education level	Special School	2 (100%)	0 (0%)	0.28*	
	Elementary School	3 (50%)	3 (50%)		
	Junior High School	1 (100%)	0 (0%)		

TABLE 5. Continued

Variable		Verbal Recognition Memory Score Changes			RR (95% CI)
		Increase/Keep	Decrease	*p*	
	Senior High School	13 (52%)	12 (48%)		
	College	16 (76.2%)	5 (23.8%)		
Interictal EEG Wave	Normal	14 (66.7%)	7 (33.3%)	0.70*	
	Slow general/focal	6 (75%)	2 (25%)		
	Ipsilateral focal epilepsy	5 (55.6%)	4 (44.4%)		
	Bilateral/generalized	8 (53.3%)	7 (46.7%)		
	Epilepsy/± slow wave				
Number of AED	Mean	2.26 ± 0.92	2.44 ± 1.10	0.65€	
	Median	2 (1–5)	2 (1–5)		
Lesion Side	Right	20 (83.3%)	4 (16.7%)	0.008$	1.722 (1.148–2.583)
	Left	15 (48.3%)	16 (51.6%)		
IQ score	Mean	88.11 ± 17.93	87.55 ± 13.15	0.90&	
	Median	93 (47–110)	91.5 (54–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test
AED : Anti epileptic drugs, EEG : Electroencephalography; IQ : Intelligence of Quotient

TABLE 6
Bivariate Analysis on the Relationship of Clinical Demographic Variables with Visual Memory Construction Recall Score Change

Variable		Visual Memory Construction Recall Score Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
Age of onset	Mean	14.19 ± 7.40	12 ± 1.69	0.54€	
	Median	13 (1–36)	12 (10–15)		
Ill duration	Mean	13.64 ± 8.80	14.75 ± 9.47	0.79€	
	Median	12 (3–34)	11 (4–29)		
Seizure Frequency	Often	29 (80.6%)	7 (19.4%)	0.35*	
	Moderate	14 (93.3%)	1 (6.7%)		
	Infrequent	4 (100%)	0 (0%)		
Education level	Special School	2 (100%)	0 (0%)	0.07*	
	Elementary School	4 (66.7%)	2 (33.3%)		
	Junior High School	0 (0%)	1 (100%)		
	Senior High School	23 (92%)	2 (8%)		
	College	18 (85.7%)	3 (14.3%)		
EEG interictal	Normal	18 (85.7%)	3 (14.3%)	0.57*	
	Slow general/focal	7 (87.5%)	1 (12.5%)		
	Ipsilateral focal epilepsy	9 (100%)	0 (0%)		
	Bilateral/generalized	12 (80%)	3 (20%)		

TABLE 6. Continued

Variable		Visual Memory Construction Recall Score Change			RR (95% CI)
		Increase/Keep	Decrease	*p*	
	Epilepsy/± slow wave				
Number of AED	Mean	2.27 ± 1.01	2.63 ± 0.74	0.17€	
	Median	2 (1–5)	2.5 (2–4)		
Lesion Side	Right	22 (91.7%)	2 (8.3%)	0.25$	1.137 (0.921–1.403)
	Left	25 (80.6%)	6 (19.4%)		
IQ score	Mean	89.74 ± 15.05	77.13 ± 19.69	0.041&	
	Median	94 (50–110)	79 (47–110)		

Description: $p<0.05$ significant, €Mann Whitney test, *Pearson Chi Square, $Chi Square, &Independent T test

impaired memory function.

In preoperative conditions, dominant verbal disturbances were the most common form of disturbance in both the left and right-sided sclerosis groups (65.9% and 48.8%) where the verbal memory index was lower than the visual memory index, especially in patients with left sclerosis.[19] Visual memory impairment was only observed in 11.6% of patients with right-sided sclerosis and 7.3% of patients with left-sided sclerosis. In the postoperative condition, memory index improvement was found in 23.3–36.6% of patients where memory improvement was found to be similar between left and right sided hippocampal sclerosis and between verbal and visual domains.[19] Impaired verbal memory was the most common disorder found in patients with ELT caused by hippocampal sclerosis both on the left and right side. Hippocampectomy can improve the memory index in ELT patients regardless of the side of surgery or the domain of impaired memory function.

There was a significant relationship between IQ scores and visual memory construction recall changes. Patients with high IQ scores experienced an increase in visual memory construction recall or persisted. Furthermore, Rzezak (2017) showed that calculating IQ differences between patients and controls impact the cognitive impairment profile observed in TLE children and adolescents with short- and long-term memory deficits and semantic memory.[20] Furthermore, people with higher intelligence may have less cognitive dysfunction associated with brain pathology. Patients with high IQ showed better immediate visual memory before surgery than those with average and no post-operative changes. Surgery did not impact those with high IQ in verbal fluency and memory, showing that cognitive reserve positively affects function, even after TLE surgery.[21]

Limitations in this study were the non-uniform post-operative evaluation period, unanalyzed subjects due to incomplete data on hippocampal preparations, subjects who refused to be studied and living far from the referral hospital.

CONCLUSION

There is a significant relationship between age of onset and changes in verbal recognition memory scores, as well as IQ and changes in visual recall memory scores. Multivariate analysis found that the lesion location on the dominant side affected changes in verbal recognition memory scores.

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Original Article

Mean Platelet-Lymphocyte Volume Ratio as Predictors of Coronary Artery Severity in Chronic Coronary Syndrome

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Abstract

Background : The increase in platelet aggregation and inflammation play an essential role in atherosclerosis. Furthermore, the level of activity depends on their size, with larger platelets facilitating the thrombosis process. Severe Coronary Artery Disease (CAD) is associated with low lymphocyte count. It is also linked with Mean platelet volume [MPV], Platelet Lymphocyte Ratio [PLR], and Mean Platelet Volume to Lymphocyte Ratio [MPVLR]. This study aims to investigate MPV, PLR, and MPVLR as predictors of the severity of Coronary Artery Lesion in Chronic Coronary Syndrome (CCS) using the Gensini score.

Methods : This is a cross sectional study conducted in Dr. Kariadi General Hospital, involving a total sample of 68 respondents. Furthermore, CCS were evaluated before conducting coronary angiography. The study comprises of two group of patients divided according to their Gensini scores, namely mild and severe, for ≤ 20 and > 20, respectively. MPV, PLR, and MPVLR were then compared between the two groups.

Results : At a cut-off level of 3.4, MPVLR predicted the coronary artery severity with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value of 80%, 50%, 82%, and 47% (area under the curve [AUC] 0.67; 95% confidence interval [CI], 0.52–0.82; p 0.029). Meanwhile, its value ≥3.4 has OR 1.55; 95% CI, 0.99–2.43; p 0.034.

Conclusion : This study conclude that MPVLR ≥3.4 can be used as a predictor of Coronary Artery Lesion Severity based on the Gensini score in CCS cases.

Keywords : Chronic Coronary Syndrome, Gensini Score, Mean Platelet Volume, Mean Platelet Volume to Lymphocyte Ratio, Platelet Lymphocyte Ratio

INTRODUCTION

The most leading cause of death in the world is cardiovascular disease suffered by 18.6 million people in 2019. Its primary significant contributor is Coronary Artery Disease (CAD), with 9.14 million mortality.[1] The 2016 report from the Heart Disease and Stroke Statistics Update stated that the number of people with CAD in the United States was 15.5 million which is 6.2% of the adult population, where 8.2 million had angina pectoris and 7.6 million experienced myocardial infarction.[2] According to Basic Health Research (Riskesdas), there is an increase in the prevalence of this disease in Indonesia from 0.9% in 2013 to 1.5% in 2018. Furthermore, the region with the highest incidence of 1.6% was the Central Java province.[3]

Chronic inflammation and thrombosis are crucial causes of atherosclerosis.[4,5] Furthermore, activated platelets express adhesion, coagulation, and inflammation mediators. This triggers the steady progression of plaque formation, thrombosis, and atherosclerosis. Low-Density Lipoprotein (LDL), when accumulated in its oxidized form, can stimulate a chronic inflammatory process characterized by the lymphocytes and monocytes migration to the tunica intima of blood vessels, resulting in atherosclerotic plaques.[4,5] The platelet activation and inflammatory markers, such as P-selectin, as well as interleukins and High Sensitivity C-Reactive Protein (hs-CRP), can assess the prognosis of the CAD severity.[6–8] However, their examination process is still expensive. The degree of severity depends on the number of coronary lesions and the stenosis intensity. These can be detected by coronary angiography as a gold standard examination.

Mean Platelet Volume (MPV) is the measurement of platelet activity. Larger platelets tend to have higher activity and are more pro-thrombotic than their small counterpart, which plays an essential role in atherosclerosis pathogenesis.[9–11] High MPV has increased platelet aggregation, thromboxane production, adhesion molecules expression, and β-thromboglobulin production. Furthermore, its higher values is experienced among patients with CAD risk factors such as hypercholesterolemia, diabetes mellitus, smoking, hypertension, atrial fibrillation, obesity, and cerebrovascular disease.[10,12–16] This was related to the prevalence of Acute Myocardial Infarction (AMI) as well as the Major Adverse Cardiac Events (MACE) prognosis. Additionally, MPV value can be used as a prognostic predictor of death in CAD and the severity of the coronary lesions.[16]

Examination of the Platelet Lymphocyte Ratio (PLR) describes the platelet aggregation and inflammation level in patients with coronary atherosclerosis. Its elevated levels are common in various heart problems, including unstable angina and coronary syndromes (acute or chronic), such as *ST-elevation myocardial infarction* (STEMI) and *Non-ST-elevation myocardial infarction* (NSTEMI). This is closely related to the prevalence of severe atherosclerosis, MACE, more frequent post-angiographic no-reflow events, and increased mortality risk from any cause.[13,17,18]

Mean Platelet Volume to Lymphocyte Ratio (MPVLR) has been used in several previous studies as a prognostic biomarker for various conditions, including malignancy, stroke, cystic fibrosis, pulmonary embolism, chronic obstructive pulmonary disease, and some cardiovascular disorders.[19–21] In existing studies, it shows a positive correlation with no reflow after percutaneous coronary angiography, poor angiography results, death from various causes within 30 days, and mortality due to myocardial infarction within 1 year.[19,20] Therefore, this study aims to determine the ability of MPV, PLR, and MPVLR values to predict coronary artery lesions severity in Chronic Coronary Syndrome (CCS) using the Gensini Score.

METHODS

1. Observational Study

The method used was observational analytic with a cross-sectional design conducted at Dr. Kariadi General Hospital, Semarang, from November 2021 to March 2022. The inclusion criteria are Chronic Coronary Syndrome (CCS) patients aged >18. Meanwhile, patients with Acute Coronary Syndrome (ACS), a history of coronary intervention, Coronary Artery Bypass Graft surgery (CABG), and heart valve disease, were excluded from the study subjects. It also applies to those with a history of liver cirrhosis, severe infection or sepsis, acute infection, tuberculosis, Chronic Obstructive Pulmonary Disease (COPD), Chronic Inflammatory Disease, Thromboembolic Disease, Autoimmune Disease, malignancy, chronic kidney disease (CKD) Stage IV- V, and NYHA (New York Heart Association) CHF (Congestive Heart Failure) class III-IV. Similarly, this study excluded patients with hematological disorders such as aplastic anemia, leukemia, thrombocytopenia, polycythemia vera, pregnancy, and incomplete data.

2. Laboratory Analysis

The independent variables such as MPV, PLR, and MPVLR, were examined with an automated hematology analyzer SYSMEX XN 1000 with the principle of laser flow cytometry. It was checked 20–30 minutes after the blood was drawn and treated with a citrate anticoagulant. The MPV variable with fL units, was obtained from the direct analysis results of the hematology analyzer machine. The PLR variable was measured using the following formula of Platelets (uL) / Number of lymphocytes (% lymphocytes x number of Leukocytes

(uL)). Meanwhile, MPVLR was calculated by dividing MPV (fL) with Number of lymphocytes (%lymphocytes x number of Leukocytes (uL)) with units (fl / (10^3/µL)).

3. Gensini score assessment

The dependent variable in this study is CCS which is assessed by the Gensini score and grouped into severe and mild, with > 20 and ≤20, respectively. The Gensini score is measured by multiplying each stenotic lesion severity degree with the multiplication factor for each lesion based on the location. Subsequently, the sum of all lesion severity scores was determined.

4. Statistical Analysis

Primary data was obtained from the results of the examination conducted at the Clinical Pathology Laboratory of Dr. Kariadi General Hospital. They were then analyzed using the IBM SPSS Statistics 25 Program. Furthermore, their distribution was tested using the Kolmogorov–Smirnov test to assess normality. The mean value and standard deviation (SD) was used to report the quantitative variables with normal distribution. Variables with non-normal distribution will be reported using the median value, while categorical variables will be presented as numbers and percentages. The Spearman test calculates the correlation coefficient of MPV value with PLR and MPVLR based on Gensini score. It is considered statistically significant when p<0.05. The cut-off point value was taken from the Receiver Operating Curve (ROC) analysis of the MPV, PLR, and MPVLR values for the CCS severity category. The results are presented in the form of a sensitivity value (true positive / (true positive + false negative) x 100%), specificity (true negative / (true negative + false positive), positive predictive value (true positive / (true positive + false positive) x 100%), and Negative Predictive Value (true negative / (false negative + true negative) x 100%). Risk estimation was also performed between the MPV, PLR, and MPVLR values. This study was approved by the Medical and Health Research Ethics Commission (MHREC) at Dr. Kariadi General Hospital with number 991/EC/KEPK-RSDK/2021.

RESULTS

There were 68 respondents in this study, which comprises of 48 men and 20 women. They have mean age of 58.47, with 36, 52, 21, 40, 14, and 21 people having comorbid obesity, hypertension, Diabetes Melitus (DM), dyslipidemia, smoking, and smoking history, respectively, as shown in Table 1.

The respondents were divided into 2 categories of 50 severe and 18 mild people. The severe Gensini group consist of 79.2% male, with an average age of 58.78. Furthermore, it is dominated by comorbidities of obesity, hypertension, DM, dyslipidemia, and smoking (p>0.05). It has lowere median platelet and mean absolute lymphocyte counts (249.5 vs. 303; p 0.02 and 2.4 vs. 2.73; p 0.068). Additionally, the MPVLR values were significantly higher (p 0.029), while MPV and PLR values were insignificantly higher (p>0.05), as presented in Table 2.

The mean age in the severe and mild Gensini groups are 58.78 and 57.61. However, there are 35 and 9 people, respectively, in the severe and mild Gensini group that are ≥55 years, as shown in Figures 1 and 2.

The Spearman test analysis shows a significant positive correlation between the MPV value and the CCS severity (R 0.271; P 0.025). There is also a significant negative correlation between the number of platelets and the CCS severity (R -0.304; P 0.012), as shown in Table 3.

Using the ROC chart, the study calculated the cut-off point for the most optimal MPV value as a predictor of the CCS severity. According to the analysis, the area under the curve was 63% (95% CI 4779) with p value of 0.094. Furthermore, the optimum MPV cut-off point was

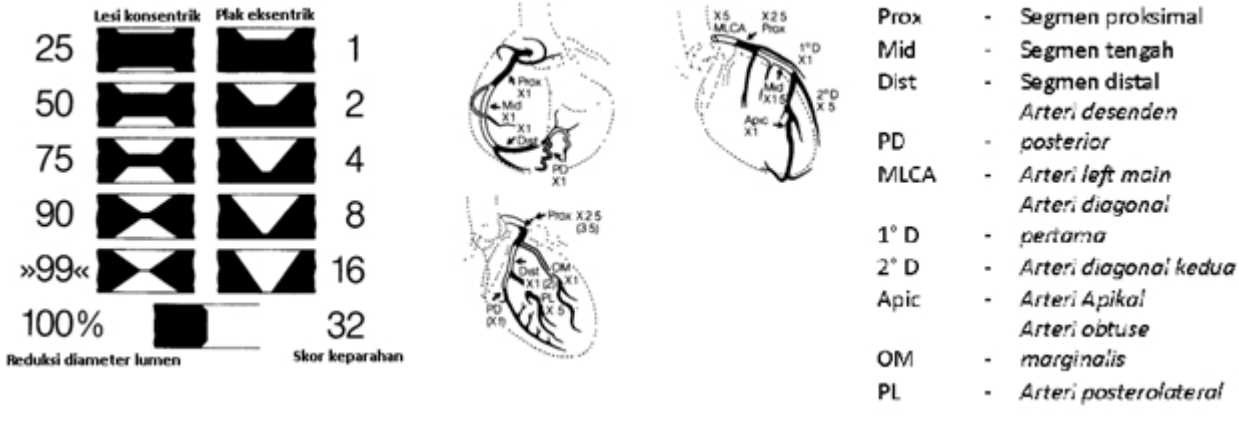

Figure 1. Gensini scoring system[21]

TABLE 1
Characteristics of study subjects

Variable		N (%)	Mean (SD)	Median	Minimum–Maximum
Gender	Male	48 (70.6)			
	Female	20 (29.4)			
Age			58.47 (7.106)		
Obesity		36 (44.1)			
Hypertension		52 (76.5)			
DM		21 (30.9)			
Dyslipidemia		40 (58.8)			
Smoking status	Smoking	14 (20.6)			
	No smoking	36 (52.9)			
	Have a smoking history	18 (26.5)			
Platelet count				262.000	(155.000–464.000)
MPV (fL)			9.997 (1.038)		
Absolute Lymphocyte Count (10^3/µL)			2487 (0.797)		
PLR				112.79	(54.13–282.93)
MPVLR (fl /(10^3/µL))			4.442 (1.513)		
Gensini Score					(2–190)

DM diabetes mellitus, MPV of mean platelet volume, PLR platelet count to lymphocyte count ratio, MPVLR mean platelet volume to lymphocyte count ratio.

TABLE 2
Characteristics of subjects according to Gensini score category

Characteristics		Severe Gensini (N 50)	Mild Gensini (N 18)	p
Gender, n (%)	Male	38 (79.2)	10 (20.8)	0.183
	Female	12 (60)	8 (40)	
Age, mean [SD]		58.78 [6.914]	57.61 [7.755]	0.495
BMI, N (%)	Obesity	21 (70)	9 (30)	0.757
	Not obese	29 (76.3)	9 (23.7)	
Hypertension, N (%)		36 (69.2)	16 (30.8)	0.261
Diabetes mellitus, N (%)		14 (66.7)	7 (33.3)	0.576
Dyslipidemia, N (%)		29 (72.5)	11 (27.5)	1
Smoking status, N (%)	Smoke	11 (78.6)	3 (21.4)	0.379
	Smoking history	15 (83.3)	3 (16.7)	
Platelet count (10^3/µL),		249.5	303	0.02
Median (minimum–maximum)		(155–464)	(186–407)	

TABLE 2. Continued

Characteristics	Severe Gensini (N 50)	Mild Gensini (N 18)	p
MPV (fL), Mean [SD]	10.11 [0.963]	9.69 [1.201]	0.09
Absolute Lymphocyte Count (10^3/µL), Mean [SD]	2.4 [0.813]	2.73 [0.719]	0.068
PLR, Mean [SD]	122.4 [45.73]	121.24 [48.18]	0.646
MPVLR (fl /(10^3/µL)), Mean [SD]	4.65 [1.49]	3.88 [1.44]	0.029

BMI body mass index, MPV mean platelet volume, PLR ratio of platelet count to lymphocyte count, MPVLR ratio of mean platelet volume to lymphocyte count

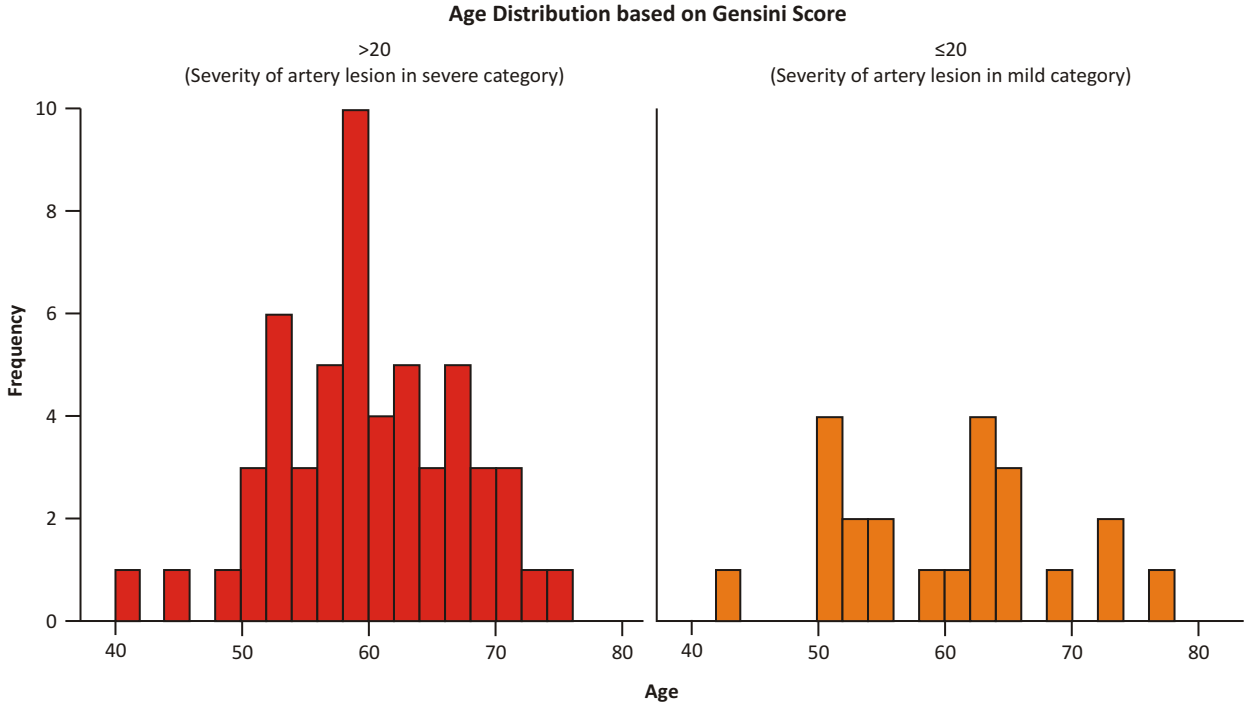

Figure 2. Graph of age comparison by Gensini score category

9.75 fl with sensitivity, specificity, PPV, and NPV of 60% sensitivity, 61%, 81%, and 35%, respectively (OR 1.26; 95% CI 0.93–1.70; p 0.205), as presented in Figure 3.

The PLR value has an insignificant negative correlation with the CCS severity (r -0.057; p 0.645). However, no significant relationship was observed between the PLR value and the CCS severity. The hypothesis showed that no further statistical tests were conducted.

The MPVLR value has an insignificant positive correlation with the CCS severity (r 0.217; p 0.076). Furthermore, there is a significant difference between the MPVLR values of the severe and mild groups.

Using the ROC chart, the cut-off point for the MPVLR value to be used as a predictor of the CCS severity was calculated. A statistically significant ROC value of 67% (95% CI 5282) was obtained for the MPVLR score (p 0.029). Subsequently, the optimum value was 3.4 with sensitivity, specificity, PPV, and NPV of 80%, 50%, 82%, and 47% (OR 1.55; 95% CI 0.99-2.43; p 0.034).

DISCUSSION

Based on characteristics data, it was discovered that the severe Gensini group was dominated by males at 79.2% with a mean age of 58.78. Its MPV, PLR, and MPVLR values were higher than those in the mild Gensini group (MPV 10.11 vs. 9.69; PLR 122.4 vs. 121.24; MPVLR 4.65 vs. 3.88). Finally, it also exhibit a lower absolute lymphocyte count.

A low lymphocyte count was also shown in previous studies in patients with ACS and stable

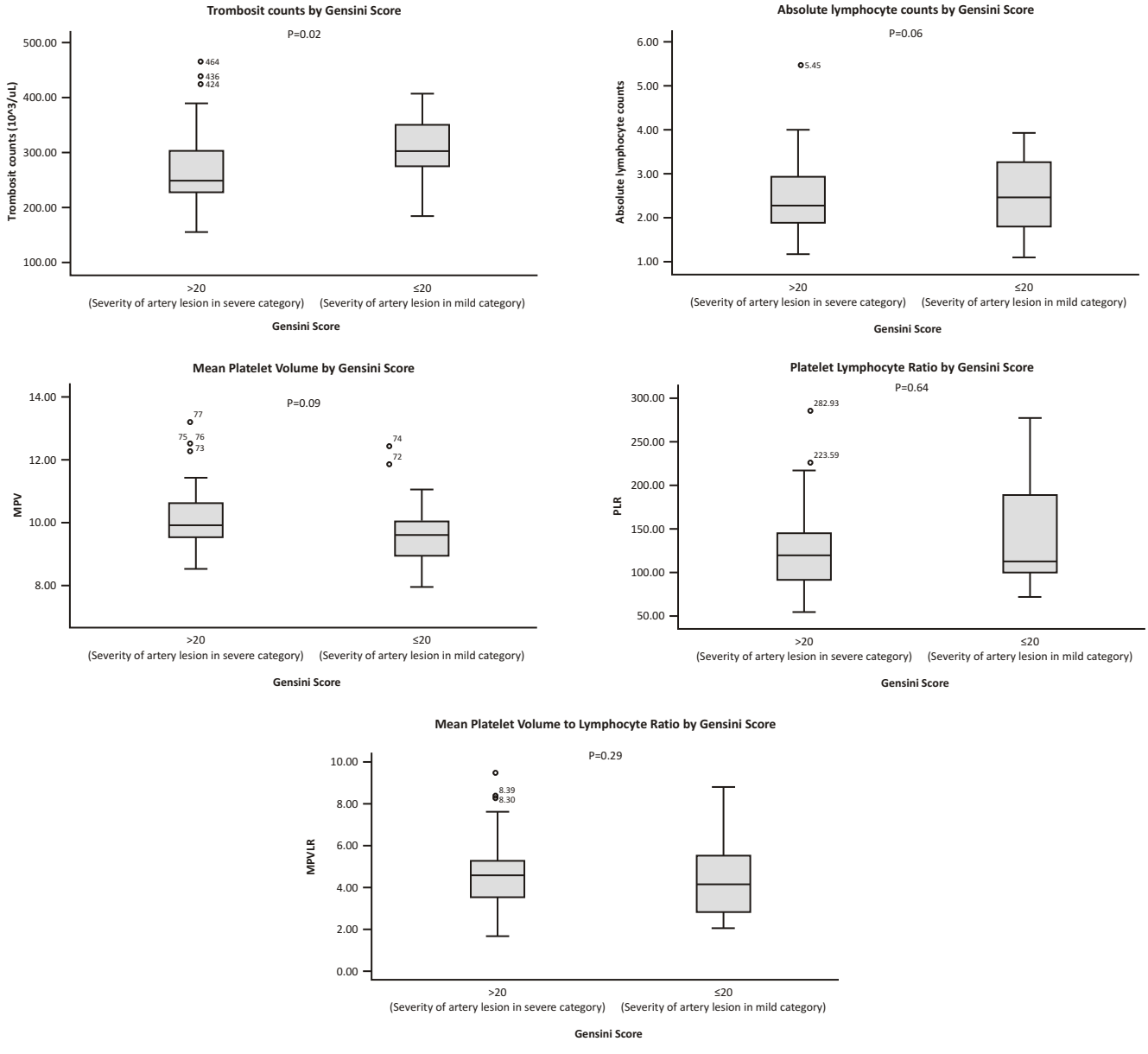

Figure 3. Graph of variable platelet count, absolute lymphocyte count (ALC), MPV, PLR, and MPVLR values according to the Gensini score category

CHD.[13,17,22,23] This is because the inflammatory process plays an essential role in atherosclerosis, from initiation to thrombosis. Furthermore, the low lymphocyte count was due to increased steroid levels associated with physiological stress, increased inflammatory response, and elevated lymphocyte apoptosis.[13,24]

In this study, the platelet count of the severe Gensini group was significantly lower than its mild counterpart ($p<0.05$). Spearman test showed a negative correlation between the number of platelets and the Gensini score (r - 0.304; p 0.012). This result is inconsistent with previous studies on stable CHD patients, in which the severe group had higher mean platelet counts and mean age (63–64 years) than its mild counterpart.[13,22,23] The decrease in platelet count in the severe Gensini group could be due to the predominance of 35 subjects aged ≥55. Furthermore, it is generally relatively stable at 25–59 years, reduced significantly 10x103/µL at 60–69 years, and decreased 20×103/µL at the age > 69 years.[25]

There is a significant positive correlation between the MPV value and the CCS severity, namely r 0.271 ($p<0.05$). This follows previous studies in which the MPV value correlated significantly with the Gensini score in CHD patients undergoing elective angiography.[12,16,26] It is because large platelets store more granules and mitochondria per unit volume, have a greater capacity to secrete inflammatory mediators, and express more receptors per unit membrane area, hence, they are more

TABLE 3
Spearman correlation between age, platelet count, absolute lymphocyte count, MPV, PLR, MPVLR values, and Gensini score

Parameter	R	P
Age	0.089	0.469
Platelet count (10^3/µL)	-0.304	0.012*
Absolute Lymphocyte Count (10^3/µL)	-0.140	0.256
MPV (fL)	0.271	0.025*
RLR	-0.057	0.645
MPVLR (fl /(10^3/µL))	0.217	0.076

MPV of mean platelet volume, PLR ratio of platelet count to lymphocyte count, MPVLR mean ratio of platelet volume to lymphocyte count,
*P < .05 was considered statistically significant

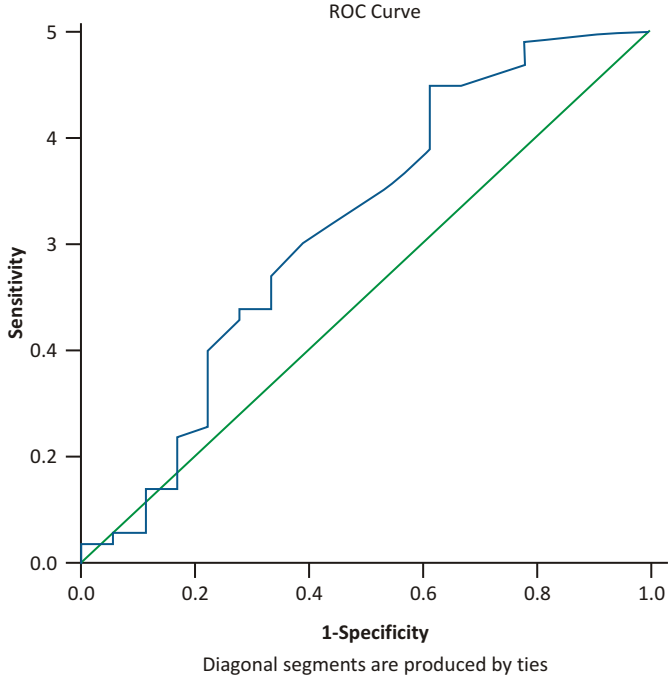

Figure 4. Graph of ROC between the MPV value and the severe Gensini score

atherogenic.[12,13,16,26] In contrast to previous cohort studies on diabetic patients undergoing coronary angiography, it was discovered that the MPV value was significantly related to age, inversely proportional to the platelet count, and was not related to P-selectin as a marker of platelet reactivity in CHD patients.[27]

The MPV value of 9.75 fl has a sensitivity, specificity, PPV, and NPV of 60%, 61%, 81%, and 35%. Despite having a good level of sensitivity and specificity, statistically based on the p-value and 95% CI, the variable cannot predict coronary syndrome severity (OR 1.26; 95% CI 0.93-1.70; p 0.205). Furthermore, other studies have shown different results; namely, the MPV value can be used as a predictor of the coronary complex lesions incidence in stable angina.[26]

In this study, the PLR values were negatively correlated with the CCS severity but not significant (r -0.057; p>0.05). It was previously reported that the PLR value was positively correlated and significantly different from the CCS severity.[13,22,23] The difference in this study was that there were 35 subjects aged ≥55 in the severe Gensini group compared to the 9 in its mild counterpart, accounting for 79% vs. 21%.

Trakarnwijitr *et al*. stated that there was a significant relationship between high PLR values ≥146.7 and an increased incidence of CAD (stenosis ≥50%) in patients aged ≥55.27 In CAD patients, P-selectin levels decreased at age >65 and increased at <55. They are

TABLE 4
Diagnostic test of MPV value as a predictor of CCS severity

	Severe Gensini	Mild Gensini	Total
MPV ≥9.75	30	7	37
MPV <9.75	20	11	31
Total	50	18	68

Sensitivity 60%, Specificity 61%, PPV 81% , NPV 35%

TABLE 5
Diagnostic test of MPVLR value as a predictor of CCS severity

	Severe Gensini	Mild Gensini	Total
MPVLR ≥3.4	40	9	49
MPVLR <3.4	10	9	19
Total	50	18	68

Sensitivity 80%, Specificity 50 %, PPV 82 %, NPV 47

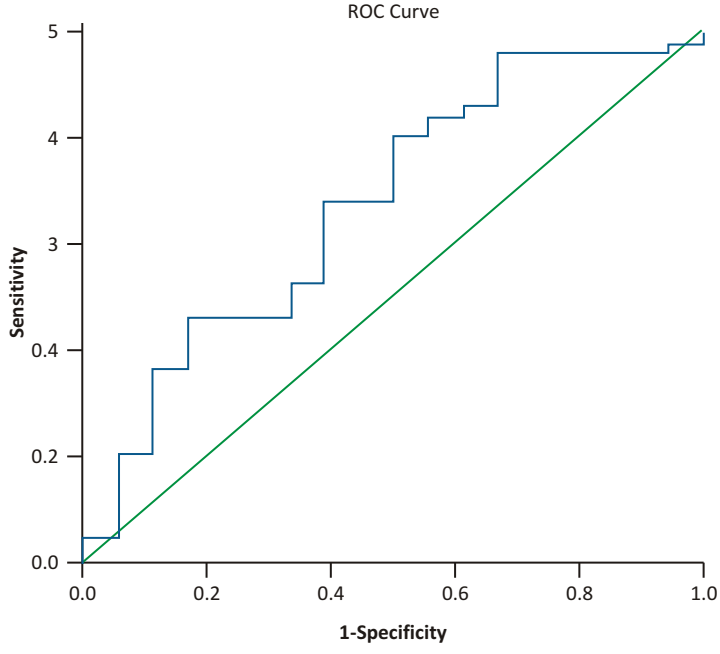

Figure 5. Graph of ROC between MPVLR values and severe Gensini scores

known to be positively correlated with the Gensini score and increase according to the number of coronary lesions involved.[28] Furthermore, P-selectin levels are known to be positively correlated with platelet counts.[29] The PLR values in this study were unrelated to the CCS severity. However, previous report stated that it is an independent predictor with OR 1.043; KI 1.036-1.049).[22]

P-selectin is a granular membrane protein secreted by α-granules in platelets. It roll and stick platelets to endothelial cells' surface and is activated in atherosclerosis. Therefore, it can be used as a marker of platelet activation.[28,29] The PLR values in this study were not related to the CCS severity. However, previous studies stated that PLR is an independent predictor with an OR of 1.043; KI 1.036–1.049).[22]

The correlation between the MPVLR value and the Gensini score was insignificant (p 0.076; r 0.217). A statistically significant difference in MPVLR values was found (p 0.029) when comparing the heavy and mild CCS groups. Studies on the relationship between the value

and the degree of CCS severity measured using the Gensini score have never been conducted. Previous reports also stated that patients with poor coronary circulation would have higher MPVLR values ($p < 0.001$) than coronary collateral circulation in those with stable angina pectoris/CCS.[19] Coronary collateral circulation is affected by several factors, such as the duration and severity of coronary stenosis, endothelial dysfunction, hypertension, DM, dyslipidemia, and smoking.[30] Finally, laboratory indicators such as platelet count (282.1 vs. 261.7), lymphocyte count (1.8 vs. 2), PLR value (156.8 vs. 132.1), and mean platelet volume (MPV) also differ significantly between stable angina patients with poor and good coronary collateral circulation (8.3 vs. 8).[31–33]

The MPVLR value of 3.4 has a sensitivity, specificity, PPV, and NPV of 80%, 50%, 82%, and 47%. Patients with values ≥ 3.4 were 1.55 times at risk (95% CI 0.99-2.43; p 0.034) of experiencing complex coronary lesion events. The disadvantage of this study is that it has limited sample and was conducted in one place, hence, the data obtained is less diverse. Furthermore, there is no molecular explanation regarding the relationship between variables with future prognosis. As a result, further studies is needed with a larger population and conducted in many places to deepen the understanding of the mechanism. It also makes the MPVLR value a predictor that can be applied in daily.

CONCLUSION

MPVLR can be used as a predictor of the severity of Chronic Coronary Syndrome. Its value of 3.4 has a sensitivity, specificity, PPV, and NPV of 80%, 50%, 82%, and 47% for complex coronary lesions in CCS patients. Furthermore, MPVLR value ≥ 3.4 has been shown to reperesent a 1.55 times greater risk of complex coronary lesions.

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Original Article

Comparison of Combination of Foot Exercise with and without Hydrotherapy to the Range of Motion on Active Knee Joints and Ankle Joints in The Elderly

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Abstract

Background : Aging results in a decrease in various body functions, one of them is in the aspect of mobility. Increasing age can reduce the range of motion of the joints. One of the easy physical activities for the elderly is foot exercise and hydrotherapy (warm water soaks) in order to minimize the decrease in ROM. This study was aimedt o compare the combination of foot exercises with hydrotherapy and without hydrotherapy on active ROM of the lower extremities in the elderly.
Methods : This research is an experimental study with parallel 3 groups pre and post-test design. The research subjects were 21 elderly people in RW 04 Karang Wetan, West Ungaran, Semarang Regency. Active ROM of the lower extremity was measured before and after intervention using a goniometer. analyzing the data of this study using the Paired T test and One Way ANOVA method.
Results : There was no significant increase in the active ROM of the lower extremities in the control group, p=0.114 (p>0.05). The range of active motion of the lower extremities (pre test to post test) in the combination treatment group of foot exercise and hydrotherapy p < 0.001 (p < 0.05) and the treatment group of foot exercise p = 0.001 (p <0.05) experienced a significant increase . However, there was no significant difference in the increase in active ROM of the lower extremities in the combination treatment group with foot exercises and hydrotherapy, p=1.00 (p<0.05) and the foot exercise treatment group.
Conclusion : Physical activity in the form of a combination of foot exercises with hydrotherapy and without hydrotherapy performed 3 times a week for 5 weeks has been shown to increase the active ROM of the lower extremities in the elderly. However, there was no significant difference between the two which was more effective in increasing the active ROM of the lower extremities in the elderly.

Keywords : Foot exercise, hydrotherapy, Range of Motion

INTRODUCTION

Elderly (elderly) is a person with an age of more than sixty years.[1] The number of elderly people in 2014 was 18.781 million people and is predicted to increase to 36 million people in 2025.[2] The percentage of elderly people in Indonesia has increased by around 25 million people or around 9.6% in a span of almost five decades (1971–2019).[3] Aging is a continuous process that causes cumulative changes in which the immune system declines in response to internal stimuli as well as external.[2] Aging occurs due to the accumulation of various kinds of cellular and molecular damage over time which will cause a gradual decline in mental and physical capacity, an increased risk of disease and death.[4] In the aging process, body composition will change, including a reduction in muscle mass, an increase in body mass, centralization of fat, and an increase in intramuscular fat.[5] Loss of muscle fiber in the elderly is due to atrophy of myofibrils and replacement of fibrous tissue that begins in the fourth decade of life.[14] Diseases that often occur in the elderly include hypertension, osteoporosis, visual and hearing impairment, dementia, etc. One aspect affected by the aging process is joint flexibility.[2] Decreased joint flexibility has the potential to affect normal functions in everyday life, such as dressing, reaching for objects, maintaining a normal gait and for activities that involve bending and reaching down. While loss of flexibility with age is often caused by a decrease in physical activity.[6] *Range of Motion* (ROM) is one of the physical indicators related to the role of the movement function. Range of Motion (ROM) is defined as the maximum degree of movement in a particular joint.[7] Active ROM is the range of motion that can be achieved when the muscles are contracted and the antagonist muscles are relaxed. Active ROM is achieved when the opposing (antagonist) muscles contract and relax, resulting in joint movement.[15] Some causing Range of motion reduction in the elderly includes related connective tissue restructuring, age genetics, trauma, diseases such as arthritis, and reduced activity levels.[16] Knee joint ROM includes flexion and extension movements. The ankle joint ROM includes dorsiflexion, plantarflexion, inversion and eversion.

Gymnastics is a body exercise that is made and selected with a plan that is arranged systematically with the aim of forming and developing a harmonious personality.[9] Foot gymnastics a purposeful leg exercise that increase blood circulation and strengthen the small leg muscles and strengthen the calf muscles, thigh muscles and reduce the limitations of joint movement.[10] Hydrotherapy, formerly known as hydropathy, is a method of therapy by utilizing water as a medium to treat or relieve pain.[11] Warm water has a good physiological impact on the body, including improving blood circulation, stabilizing blood flow and heart function. The loading factor in the water can also increase the strength of the muscles and ligaments associated with the body's joints.[12]

Therefore, this study was conducted to determine the effect and comparison of foot exercises with hydrotherapy and without hydrotherapy on active ROM of the knee and ankle joints.

METHODS

This research is a Quasy experimental research using 3 parallel groups pre and post test design with control group method.The research subjects used in this study were the elderly in RW 04 Karang Wetan, West Ungaran, Semarang Regency who were selected by purposive sampling based on inclusion and exclusion criteria.

The inclusion criteria are (1) Elderly and domiciled in RW 04 Karang Wetan, West Ungaran, Semarang Regency, (2) aged 60–80 years, and (3) willing to participate in the study by filling out and signing an informed consent form. The exclusion criteria for the research subjects were (1) unable to speak, unable to hear, unable to see, (2) unable to use and understand Indonesian, (3) had a psychiatric disorder, and (4) had a disability. The research subjects were grouped into three groups: treatment group 1 (combination of foot exercise with hydrotherapy), treatment group 2 (foot exercise), and the control group. The treatment group was given intervention for 5 weeks with a frequency of 3 times a week.

The foot exercise intervention was carried out for 9 minutes which was demonstrated live with video guidelines and direct directions from the researcher. The hydrotherapy intervention of soaking the feet using warm water was carried out for 15 minutes which was divided into 2 sessions namely, soaking in the first minute then resting 1 minute by removing the feet from the bucket, then putting them back in the bucket for the second 7½ minute. Performed 3 times a week for 5 weeks.

Measurement of active ROM of the knee and ankle jointsusing a goniometer to measure the range of motion of the joints actively in both feet. Measured ROM is at the knee joint (Articulatio Genu) namely flexion and extension movements. The ankle joints (Articulatio Talocruralis) that are measured are dorsiflexion, plantarflexion, inversion, and eversion. The research data are units of degrees, and the higher the number of degrees indicates the wider the range of motion of the joints. Active ROM was then totaled and accumulated for each research subject. Data analysis is descriptive analysis and hypothesis testing. To test the increase in the pretest and posttest hypothesis for each group, a paired t-test was performed and to find out the difference in increase between groups, an unpaired t-test/Oneway ANOVA with Bonferroni's post hoc was used to determine the difference in increase between groups.

Research Ethics was obtained from the Medical and Health Research Ethics Commission (KEPK) Faculty of Medicine, Diponegoro University (No. 206/EC/KEPK/FK-UNDIP/VI/2021).

RESULTS

Characteristics of Research Subject Groups

The research subjects were 21 elderly in The RW 04 Karang Wetan area, West Ungaran, Semarang Regency with the characteristics shown in Table 1.

Active Range of Motion comparison

Based on Table 2, shows the Range of Motion data pre-test, post-test, and delta (difference) based on treatment. After the data normality test was carried out, the data were found to be normally distributed p>0.05, so a paired t test was carried out. In the control group, the results of the difference test between the pre-test and post-test showed p value = 0.114, which means that there was no significant increase in the Range of Motion pre-test and post-test because p> 0.05. In the treatment group 1, namely the foot exercise group with warm water foot

TABLE 1
Characteristics of Research Subject Groups

Characteristics		Group			p
		Control (n=7)	Treatment 1 (n=7)	Treatment 2 (n=7)	
Age		65.57±3.55	65.43±8.94	61.71±2.75	0.129**
Gender	Man	4 (14%)	2 (28.57%)	0 (0%)	
	Woman	3 (42.86%)	5 (71.43%)	7 (100%)	
Height		1.64±0.06	1.59±0.04	1.61±0.04	0.211*
Weight		64±6.81	64.43±4.93	62.71±4.35	0.831*
BMI		23.76±2.18	25.35±1.78	24.24±1.52	0.400**

§Table values are mean ± standard deviation; Median (min–max) *One Way ANOVA test **Kruskal Wallis test

TABLE 2
Table of differences in active ROM of the knee joint and ankle joint pre-test, post-test, and delta based on treatment

Group	RoM		p	Delta
	Pre-test	Post test		
Treatment 1	34.01±2.87	40.47±2.43	<0.001¶*	6.45±1.74
Treatment 2	35.07±3.97	40.67±2.09	0.001¶*	5.60±2.39
Control	37.29±3.13	39.13±4.05	0.114¶	1.85±2.64
p.s	0.142§	0.588§		0.003§*

Description: * Significant (p <0.05); § One Way ANOVA; ¶ Paired t tests

TABLE 3
Post Hoc Bonferroni different test between groups

Group		p	Description
Pre-test	Post test		
Treatment 1	Treatment 2	1.000	Not significant
	Control	0.004	Significant
Treatment 2	Control	0.020	Significant

TABLE 4
Table of average active ROM of the lower extremities for each movement in the treatment group 1

Group	Right foot		Left Foot	
	Pretest	Postest	Pretest	Postest
Knee Flexion	120.51±11.83	127.43±9.90	120.86±10.04	120.86±5.55
Knee Extension	0	0	0	0
Inversion	15.86±3.76	20.71±6.58	18.14±7.69	25.71±5.25
Eversion	8.14±3.76	14.14±5.34	10.57±4.61	12.71±2.43
dorsiflexion	9.71±6.68	13.43±5.65	12.71±3.25	12.714±3.25
Plantar flexion	46.29±17.53	62.14±9.48	45.29±12.85	68.43±5.38

TABLE 5
Table of the average active ROM of the lower extremities for each movement in the 2nd treatment group

Group	Right foot		Left Foot	
	Pretest	Postest	Pretest	Postest
Knee Flexion	118.14±16.96	124.43±9.24	118.00±11.27	123.71±12.80
Knee Extension	0	0	0	0
Inversion	17.86±3.93	24.29±3.86	19.43±5.74	23.00±2.71
Eversion	7.14±2.48	12.71±2.69	9.57±3.10	13.86±3.48
dorsiflexion	9.57±5.47	16.00±5.94	11.71±7.65	18.14±4.60
Plantar flexion	50±10.13	65.43±4.61	59.43±10.18	66.43±8.79

TABLE 6
Table of average active ROM of the lower extremities for each movement in the control group

Group	Right foot		Left Foot	
	Pretest	Postest	Pretest	Postest
Knee Flexion	126.86±10.70	126.86±14.57	124.86±6.12	125.86±4.53
Knee Extension	0	0	0	0
Inversion	20.14±3.29	24.29±10.39	18.00±5.26	22.14±7.56
Eversion	9.29±2.50	9.57±2.15	10.57±6.40	11.43±4.76
dorsiflexion	12.71±6.75	15.43±5.83	15.57±4.20	14.57±3.10
Plantar flexion	54.57±9.76	54.28±9.48	54.86±11.81	65.14±39.55

soaks, it was found that the results of the difference test between the pre-test and post-test showed a p value <0.001 so that p <0.05, which means that there was an significant increase in the Range of Motion pre-test and post-test. Then in treatment group 2, namely the leg exercise group, the results of the different test between the pre-test and post-test showed a value of p = 0.001 so that p <0.05, which means that there was a significant increase in the Range of Motion pre-test and post-test .

Comparison of active Range of Motion between groups

Differences in pre-test and post-test differences between groups were tested for unpaired differences in normal distribution using the One Way ANOVA test with Post HocBonferroni. Based on Table 3, there appears to be a significant difference between the treatment group 1 and the control group with p value = 0.004 because p <0.05. There was a significant difference between the treatment group 2 and the control group with p value = 0.020 because p <0.05. However, the difference between groups 1 and 2 was not significant because the p value = 1.000.

DISCUSSION

This study showed the results of a significant increase in the active Range of Motion of the knee and ankle joints in both treatment groups, both those who were given a combination of foot exercise interventions with hydrotherapy and without hydrotherapy which were carried out routinely with a frequency of 3 times for 5 weeks. In the treatment group 1 (a combination of foot exercise with hydrotherapy) and the treatment group 2 (foot exercise) there was a significant increase in the active Range of Motion of the knee joint and ankle joint from pre-test to post-test. The results of the mean difference between pre-test and post-test in the treatment group combining foot exercise with hydrotherapy showed Range of Motion active knee joints and ankle joint higher when compared to the foot exercise treatment group, but the difference in ROM did not show a significant value between the two groups after the Bonferroni Post Hoc statistical test.

An increase in active ROM of the knee joints and ankle joints in the elderly is possible because in foot exercises there is a process of exercise or physical activity by moving the lower extremities, for example bending the knees, straightening the knees, pushing the soles of the feet forward, pulling the soles of the feet back , turning the soles of the feet inward, and turning the soles of the feet outward. This is in line with research by Filantip, Arif in 2015 which shows after training Active ROM of the lower extremities in the elderly found an increase in ROM in the movements of thigh extension, thigh flexion, knee abduction, knee adduction, knee flexion and knee extension as well as an increase in motor movement abilities.[13] The difference in this study lies in the intervention used, which in this study used active ROM exercise interventions while in this study the intervention was foot exercises with warm water immersion.

The results of this study are also in line with the research of Nindawi, *et al*. in 2021 where there was a significant increase in the range of motion of the foot joints in knee flexion, knee extension, plantarflexion, dorsiflexion and leg muscle strength in the elderly who were given active ROM exercise interventions.[17] The first difference in this study were samples, the samples in this study were elderly people with osteoarthritis while in this study were the elderly. The second difference is the frequency of interventions. In that study, active ROM exercises were carried out 5 times a day for 2 weeks, whereas in this study, foot exercise interventions were carried out with hydrotherapy 3 times a week for 5 weeks. Exercise can trigger a stimulus that can increase the chemical activity of the neuromuscular and muscular. Neuromuscular stimulation can increase the stimulus on the extremity nerves, especially in the parasympathetic system which will trigger an increase in the production of the neurotransmitter acetylcholine for muscle contraction. Exercise also triggers an increase in mitochondrial metabolism of the limb muscles which produces ATP which is used by the limb muscles as energy for muscle contraction and increased metabolism increases limb muscle strength.[18]

An increase in active ROM of the lower extremities in the elderly is also possible due to an increase in muscle strength by hydrotherapy interventions or warm baths. The higher the muscle strength, the movement in the joints will be better and more optimal. This is in line with research by Setiyawan, *et al*. in 2019 which showed that there was a significant increase in muscle strength in non-hemorrhagic stroke patients in the group given a warm bath compared to the control group.[18] The difference in this study lies in the sample used, the sample in this study were non-hemorrhagic stroke patients at dr. Soediran Mangun Sumarso Wonogiri, while the sample in this study was the elderly.

Hydrotherapy by soaking the feet in warm water occurs heat transfer from the water into the body through the feet which has the effect of increasing circulation (cells) due to the transfer of heat energy through convection (movement through liquids). This triggers vasodilation throughout the body which has a positive effect on increasing muscle strength due to increased smoothness of blood flow and increased transfer of oxygen and nutrients to brain and muscle cells. It also has an important role as a transfer of nutrients and potassium and calcium substances needed by myocytes. The increase in calcium ions in the cytoplasm occurs due to the release of more ions from the sarcoplasmic reticulum so that muscle mass can be maintained and allows for an increase in muscle strength. Increased blood circulation will increase oxygen supply to myocytes. Oxygen is required by mitochondria for aerobic cell metabolism. Aerobic cell metabolism will produce more ATP where ATP is needed for muscle contraction.[18] Increased limb muscle strength can move joints even better.

The limitation of this research is the difficulty of getting research subjects due to activity restrictions due to the existence of social distancing so that researchers are looking for alternative research subjects. In addition, researchers cannot control the daily activities of research subjects during the study.

CONCLUSION

The conclusion of this study is that the combination of foot exercises with hydrotherapy and foot exercises can increase the active Range of Motion of the lower extremities. However, no significant difference was found between the combination of foot exercises with hydrotherapy and only foot exercises. This research still needs to be done with larger subjects and a more even distribution of sexes.

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Original Article

Correlation between Preoperative Osteitis Degree with Postoperative Endoscopic Score in Chronic Rhinosinusitis

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Abstract

Background : In chronic rhinosinusitis patients, there is a subgroup of patients with persistent symptoms after treatment, who often shows bone thickening and remodeling in their paranasal sinuses and described as osteitis. Osteitis can be evaluated by several methods, one of which is the Global Osteitis Score (GOS). This study was aimed to analyse the correlation between preoperative osteitis degree with the postoperative endoscopic scores in chronic rhinosinusitis.
Methods : It was an observational study with cross-sectional design. We use GOS from CT scan before surgery and Lund Mackay's endoscopic score 4 weeks after Functional Endoscopy Sinus Surgery (FESS). The analysis performed with Spearman correlation test.
Results : There were 30 patients as subjects. There statistical analysis test between preoperative osteitis degree with post operative endoscopic score showed p = 0.296 with r = 0.197. The analysis result between risk factors for wound healing with the postoperative endoscopic score were allergic rhinitis (p = 1.000), polyps (p = 0.624), and smoking (p = 0.309).
Conclusion : There is no significant correlation between preoperative osteitis degree with the postoperative endoscopic score, but there is a tendency for a positive correlation between preoperative osteitis degree with the postoperative endoscopic score. There was no significant correlation between allergic rhinitis, polyps, and smoking habits with postoperative endoscopic score.

Keywords : Osteitis, Endoscopic score, Chronic Rhinosinusitis, Global Osteitis Score, Lund Mackay endoscopic score

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammation of the nose and paranasal sinuses mucosa that lasts more than 12 weeks. There is a subgroup of CRS patients with persistent symptoms after treatment whose often shows thickening and remodeling in their paranasal sinuses bone, which are described as osteitis. Osteitis is one of the contributing factors in postoperative CRS recurrence.[1]

Computed Tomography scan (CT scan) is currently recognized as the gold standard in radiographic examinations for the diagnosis of CRS patients. CT Scan can describe the pathology and degree of rhinosinusitis and also a guiding for paranasal sinus anatomy before Functional Endoscopy Sinus Surgery (FESS).[2] There is no gold standard diagnostic for osteitis. However, paranasal sinus CT scan is commonly used to assessed the degree of osteitis by using the Global Osteitis Score (GOS).[3]

Rhinosinusitis is a clinical disorder that includes heterogeneous infections and inflammatory conditions affecting the paranasal sinuses. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) defines chronic rhinosinusitis as sinusitis with clinical symptoms lasting more than 12 weeks. Recent research suggests that bones may play an active role in the CRS because the inflammation in CRS can spread through the Haversian system in the bones. The rate of bone change is the same as in osteitis of the paranasal sinuses in CRS. Furthermore, surgery that induces infection with either Staphylococcus aureus or Pseudomonas aeruginosa can induce osteitis and induce chronic inflammatory changes along the mucosa at a significant distance from the infection site. Therefore, osteitis may be an important factor in the spread of chronic inflammatory changes and may explain immunity to medical therapy.[1,3] Osteitis also plays a role in aggravating the degree of CRS and as a contributing factor to CRS recurrence after surgery.[4–6]

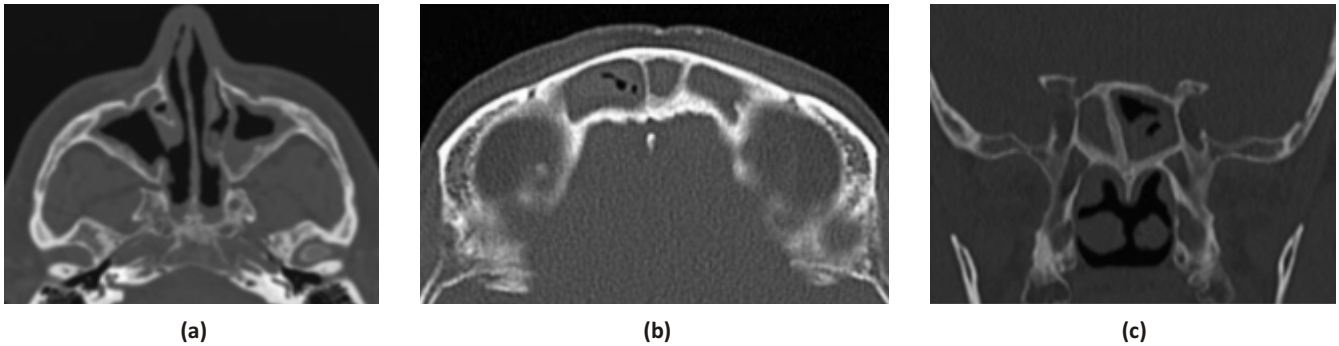
Osteitis can be diagnosed with histology and radiology examination and there were several scoring systems to examine osteitis. Although histology was considered the most accurate, but histology is more invasive because of the need for biopsy or surgery. CT scan is less invasive and have several classifications to identify osteitis (Figure 1).[3]

The diagnosis of osteitis in CRS from CT scan based on the thickness of the bony partitions in the paranasal sinuses. A recent study modified on existing classification used bone thickness and bone involvement patterns in each sinus to calculate an entirety score, called the Global Osteitis Score (GOS). This method is the most widely used in assessing the degree of osteitis.[3]

Functional Endoscopy Sinus Surgery (FESS) is a major advancement in sinus surgery for the management of CRS. This type of surgery is preferred because it is a more effective and functional conservative measure.[7] The standard post-FESS therapy according to the clinical practice guidelines in Dr. Kariadi Semarang Hospital are oral antibiotics for 5–7 days (choice of Cephalosporins, Macrolides and Quinolones), coagulant agent, analgesics, corticosteroid and nasal saline irrigation. The endoscopic evaluation performed at the first, second, and four weeks after surgery. The wound healing process evaluate with endoscopic score. The Lund Mackay endoscopic score is the most common scoring, this system based on the degree of scar tissue, crusts, edema, polyps, and secretions.[8]

Wound healing influenced by local and systemic factors. Local factors are those that directly affect the characteristics of the wound. However systemic factors are the health conditions or individual diseases that affect the wound to heal, such as allergic rhinitis, nasal polyps, and smoking.[9] Patients with a history of allergic rhinitis can experience failure in postoperative wound healing due to persistent mucociliary dysfunction. Smoking can reduce wound healing process because nicotine interferes the oxygen supply to the tissues. Polyps has high recurrency therefore it can affect the outcome of surgery.[10]

The improvement CRS after surgery can be influenced by the degree of osteitis and systemic factors. Therefore, this study is to analyze the correlation between preoperative osteitis degree with the postoperative endoscopic scores in chronic rhinosinusitis.



(a) (b) (c)

Figure 1. CT images of osteitis (a) maxillary, (b) sphenoid, and (c) frontal sinus.[3]

METHODS

It was a retrospective observational study with a cross-sectional design, using secondary data from medical record. Subject was adult CRS patient who underwent FESS in Kariadi hospital. Patient with malignant tumor were excluded. We use sample estimation for test of significance of 1 correlation, with minimal sample was 30. The preoperative osteitis degree was analyzed using GOS and the endoscopic evaluation 4 weeks after surgery using Lund Mackay endoscopic score. The risk factor for endoscopic evaluation after surgery such as diabetic, smoking, allergic rhinitis and nasal polyp were examined.

Osteitis was defined as loss of bone definition/hyperostosis/new bone formation or signal heterogeneity overlying each sinus wall. The area of the maximal thickness of each osteitis focus was measured. The grading per sinus was as follows: Grade 1: The involvement of the sinus walls less than 50% and osteitis <3 mm in width. Grade 2: The involvement of the sinus walls less than 50% and osteitis 3–5 mm wide. Grade 3: The involvement of the sinus walls less than 50% and wider than 5 mm or the involvement of the sinus walls greater than 50% and osteitis <3 mm in width. Grade 4: The involvement of the sinus walls greater than 50% and osteitis 3–5 mm wide. Grade 5: The involvement of the sinus walls greater than 50% and osteitis < 5 mm.[6]

The Lund Mackay endoscopic scores assessed mucosal inflammation, discharge, scarring, and crusting in the maxillary sinuses, ethmoid sinuses, sphenoid sinuses, frontal sinuses, and olfactory fossa with values of 0–100 (Table 1).[11]

Data was analyzed with Spearman correlation test. The research data were processed using SPSS statistical software version 26. This research was conduct after received ethical approval from the Ethics Commission with the number 553/EC/KEPK-RSDK/2020.

RESULTS

There were 30 adults patients, 18 to 57 years old. Male (57%) is often than female (43%). Preoperative osteitis degree shows the lowest score of GOS was 0 and the highest was 12, with mean score 3.27. The endoscopic evaluation 4 weeks after surgery shows the lowest Lund Mackay score of 0 and the highest 5, with mean score 1.67.

The result of the Spearman correlation test between preoperative osteitis degree (GOS) with endoscopic evaluation (Lund Mackay score) 4 weeks after surgery showed p=0.296 (p>0.001). However, the correlation was shown between the preoperative osteitis degree (GOS) with endoscopic evaluation (Lund Mackay score) 4 weeks after surgery had a positive tendency with r = 0.197 (Figure 2).

The risk factor for endoscopic evaluation after

TABLE 1
Lund Mackay Endoscopic Scoring System[11]

	Endoscopic scoring system
Polyp	0 = absence of polyps,
	1 = polyps only in middle meatus,
	2 = polyps beyond middle meatus
Oedema	0 = absent,
	1 = mild,
	2 = severe
Discharge	0 = no discharge,
	I = clear, thin discharge,
	2 = thick, purulent discharge
Eversion	0 = absent,
	1 = mild,
	2 = severe
Crusting	0 = absent,
	1 = mild,
	2 = severe

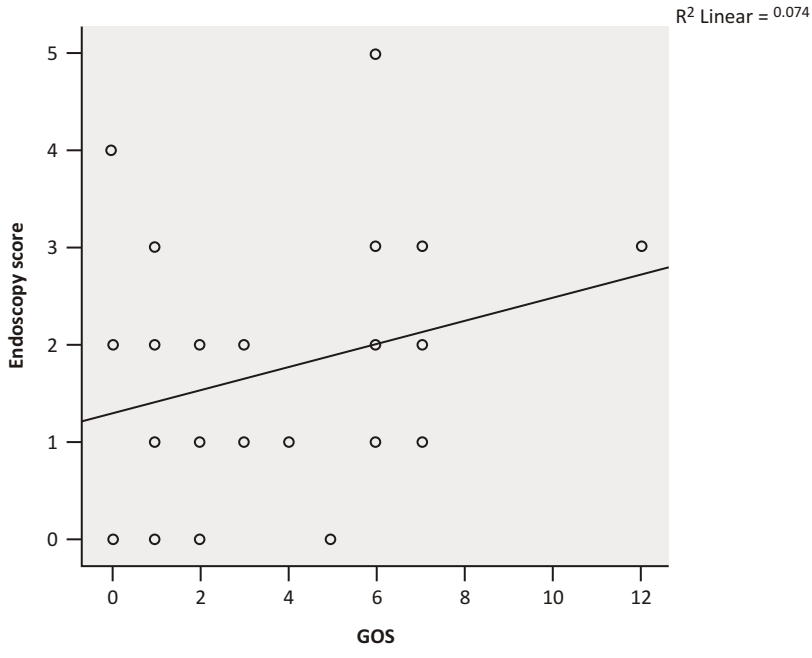


Figure 2. Correlation between preoperative osteitis degree (GOS) with endoscopic evaluation (Lund Mackay score) 4 weeks after surgery

TABLE 2
The correlation of risk factor for endoscopic evaluation after surgery with the endoscopic evaluation (Lund Mackay score) 4 weeks after surgery

Risk factors		Lund Mackay endoscopy score		p value
		Good	Not good	
Allergic Rhinitis	Yes	6	6	1,000*
	No	9	9	
Polyps	Yes	3	2	0,623**
	No	12	13	
Smoking	Yes	0	1	0,233**
	No	15	14	

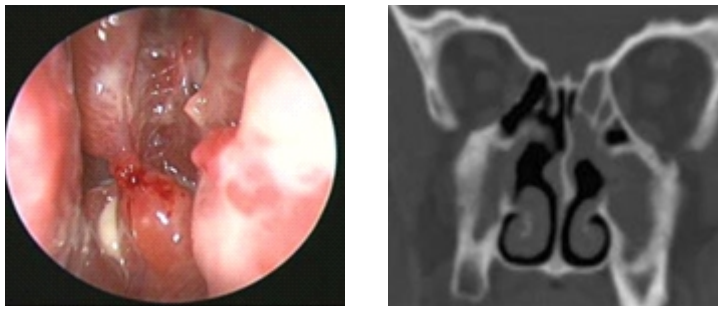
*Chi square test, ** Fisher's test

surgery that found in this study was allergic rhinitis (12), smoking (1) and polyps (5). The results of the correlation of risk factor for endoscopic evaluation after surgery with the endoscopic evaluation (Lund Mackay score) 4 weeks after surgery showed p> 0.001 (Table 2).

DISCUSSION

The incidence of CRS is commonly found in adult. The lowest age of the subjects of this study was 18 years old, while the highest was 57 years old. Similar results from previous study in Kariadi Hospital (2019) reported that the incidence of CRS is at the age range of 18–55 years old.

It has been identified that in areas of persistent mucosal disease, the underlying bone degenerates and progressing to thickening and neo-osteogenesis. This further leads to increased mucosal scarring and potential for bone adhesion. Detailed histomorphometry and histology of the ethmoid bone in human patients were performed by Kennedy *et al*.[3] Their study shows the ethmoid bone involved in CRS was found to exhibit the same histomorphometry characteristics as well-described osteomyelitis conditions in other disciplines, especially chronic sclerosing osteomyelitis of the mandible. Resolution occurs only after debridement of the underlying soft bone and osteitis, before removal can



(a) (b)

Figure 3. (a) Endoscopic view of acute exacerbation of chronic rhinosinusitis in osteitis.
(b) Coronal sinus CT scan shows hyperostotic ethmoid thickening with concomitant mucosal thickening.

usually be identified by the appearance of a persistently inflamed mucosa. Figure 3 shows the typical endoscopic appearance and CT scan in a recalcitrant CRS patient with concomitant osteitis.

This study showed that there was no significant correlation between GOS before FESS and Lund Mackay endoscopy score after FESS. This situation may occur because at the time of surgery the osteitis in CRS patients had been treated properly. Adequate postoperative therapy includes oral antibiotics, systemic corticosteroids and isotonic nasal irrigation also plays a role in wound healing after surgery. Sacks *et al*. found that the presence of osteitis was associated with the use of corticosteroids.[15] However, the correlation between GOS before FESS and Lund Mackay's endoscopic score after FESS has a positive tendency (r = 0.197), with increasing GOS scores before FESS causes Lund Mackay's endoscopic score after FESS will also increase. Snivdongs et al stated patients with Kennedy osteitis score more than 0, had greater endoscopy and CT score than those without osteitis.[16] Previous studies show there were the prevalence of osteitis in the revision ESS group is higher compare to primary ESS group, those studies stated patients with revision ESS had the highest ethmoid bone density, and a greater extent of osteitis found in patients with previous sinus surgery. However, recently the etiology of osteitis is more than a post-surgical phenomenon, there is no clear explanation why patients with primary surgery experience neo-osteogenesis. This review suggest that further studies are required to answer the unclear pathogenesis of osteitis in CRS.[17]

There are intrinsic and extrinsic risk factors for CRS that can affect the prognosis and wound healing after surgery. The clinical study in Kariadi Hospital shows the most common risk factor was allergic rhinitis.[18] Studies in tertiary referral clinics shows from 112 adult CRS patients 56.25% were atopic, 41% with asthma, and among these 53.97 were polysensitized.[19] The other study in tertiary hospital Malaysia shows a significant difference in the endoscopic scoring between both allergy and the nonallergy groups, and there were worsen edema and polypoidal degeneration of the middle turbinate on both sides in the allergy group.[20] Allergies can be in the form of allergic rhinitis, which is one of the factors causing the failure of surgery.[12] Kirtsreesakul *et al*. stated that mucocilliary dysfunction in allergic rhinitis is caused by a hypersensitivity reaction process mediated by Ig E. Allergic inflammatory mediators affect mucocilliary transport function, cilia structure and function, and mucus production that cause chronic inflammation.[13]

The second most risk factor that can affect the prognosis and postoperative wound healing in Kariadi hospital study was nasal polyp.[18] This is a benign lesion that arises from paranasal sinuses or nasal mucosal. The recurrence of nasal polyps is quite high and causes recurrent nose surgery.[14] Nasal polyps are one of the factors affecting the post-nose surgery outcome.[18] The other factor that can delayed wound healing after surgery is smoking. Hamizan *et al*. studies shows 66% subjects were diagnosed as chronic rhinosinusitis with nasal polyps (CRSwNP), and 8.93% smoked.[19] Postoperatively, smoking patients show delayed wound healing because of nicotine, carbon monoxide and hydrogen cyanide from cigarette smoke. Nicotine stimulating sympathetic nerve activity that interferes oxygen supply, releasing epinephrine causing peripheral vasoconstriction so that perfusion to the tissue decreases and causing tissue ischemia. Nicotine also reduced fibrinolytic activity and platelet augmentation causing elevation of blood viscosity. Carbon monoxide in cigarette smoke causes tissue hypoxia, by binding to hemoglobin (200 times greater than oxygen). Hydrogen cyanide can damage cellular oxygen metabolism so that oxygenation is disrupted.[9]

In this study the highest risk factor was allergic rhinitis, but for there were no significant correlation between allergic rhinitis, polyps and smoking with Lund Mackay endoscopy score after FESS. FESS is a procedure of remove the pathological mucosal tissue and bone caused by an inflammatory process, to create a conducive environment for normal mucosal regeneration. After FESS the inflammatory process due to chronic

inflammation such as allergic rhinitis, nasal polyps and smoking cessation is decrease, and the improvement of mucosal regeneration shows in endoscopy evaluation.[10]

CONCLUSION

There is no significant correlation between preoperative osteitis degree (GOS) with endoscopic evaluation (Lund Mackay score) 4 weeks after surgery, but the correlation shows a positive tendency. Allergic rhinitis, polyps, and smoking also show no significant correlation with with the endoscopic evaluation (Lund Mackay score) 4 weeks after surgery.

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Original Article

Comparison of Bacterial Pattern in Trachea and Tracheal Stoma with the Incidence of Tracheal Stoma Infection at Mohammad Hoesin Central Hospital Palembang

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Abstract

Background : Tracheostomy is a procedure to incise or make a hole in the trachea. The use of tracheal cannula leads to direct exposure of pathogens to the respiratory tract. It is necessary to identify bacterial pattern in an attempt to overcome tracheal stoma infections in order to prevent further complications. The aims of this study was to compare bacterial pattern in trachea and tracheal stoma on the incidence of tracheal stoma infection.
Methods : Observational research with a cross–sectional design. Medical record data on 60 subjects who underwent tracheal and tracheal stoma swabs and culture examination from November 2020 to October 2021 were collected. Bivariate analysis using Fischer exact test and Chi-square categorical comparative test.
Results : Sixty subjects obtained 13 species of bacteria, all identified as gram-negative bacteria. Most of the bacterial sequences and analysis of bacterial pattern were *Pseudomonas aeruginosa* (p>0.05), *Klebsiela pneumonia* (p>0.05), *Escherichia coli* (p>0.05) and *Serratia marcescen*(p>0.05) on the incidence of tracheal stoma infection**.**
Conclusion : There is no difference in the bacterial pattern of the trachea and tracheal stoma on the incidence of tracheal stoma infection.

Keywords : tracheostomy, bacterial pattern, tracheal stoma infection

INTRODUCTION

A normal trachea is protected from bacterial colonization. The trachea of healthy individuals does not contain pathogenic bacteria, or few normal bacteria/flora present. The use of tracheal cannula in tracheostomy leads to direct exposure of pathogens to the respiratory tract, and also causes a local inflammatory reaction that increases risk of infection. Infection of the tracheal stoma can be local and mild, or as extensive as to be life-threatening. Incidence of infection in tracheal stoma varies from 4% to 63% after tracheostomy. Others report the proportion of infection in tracheal stoma as much as 36% of all tracheostomy cases. Exposure to contaminated oral secretions, contaminated sputum, colonization of respiratories, and trauma from repeated manipulation of the trachea contributes to infection of tracheal stoma. Previous studies have reported 88% no bacterial growth in tracheal aspiration cultures immediately after tracheostomy, a number of 72% positive cultures on day 7 after tracheostomy. Patients with immunodeficiency such as malignancy, diabetes, malnutrition, and undergoing radiotherapy or chemotherapy, tend to be more susceptible to infection.[1–4]

Tracheal stoma infection occurs due to the presence of bacteria, which could be identified using culture examination. Tracheal stoma swab can be use to identify bacterial pattern of patients using tracheal cannula. The type of organism found is useful to determine the type of antibiotic or for administering antibiotics after the patient has an infection, in order to reduce the use of broad-spectrum antibiotics which increases the risk of resistancy. Prevention of infection is accomplished by aggressive wound care and frequent dressing changes, regular tracheal cannula replacement, and humidified air during inspiration. Knowledge and competence in handling daily care of tracheal cannula is needed to prevent further infection.[5–8] The purpose of this study is to compare bacterial pattern in trachea and tracheal stoma against the incidence of tracheal stoma infection in order to choose empiric antibiotics for patients with infections.

METHODS

This research is an observational study with a cross sectional design. The subjects of the study were all patients who underwent tracheal cannula replacement (1 to 6 months) after tracheostomy and subsequently tracheal and tracheal stoma swab in the ENT-Laryngology Division. The swab is carried out just before the new tracheal cannula is inserted using a sterile cotton swab on the mucose of the tracheal stoma, then with a different cotton swab, a swab is taken in the trachea by inserting a sterile cotton swab through the tracheal stoma and continuing it up to the trachea without touching the area around the stoma. Swabs were performed on all subjects with or without signs of infection. Tracheal stoma infection is assessed clinically in the form of swelling, redness of the skin around the tracheal stoma, thick secretions, yellow-greenish color, distinctive odor, with or without granulation tissue. Culture examination were done at the Central Laboratory Installation of RSUP Dr. Mohammad Hoesin Palembang during November 2020 to October 2021 period. The inclusion criteria includes results of swab cultures on the trachea and tracheal stoma that showed bacteria growing and complete medical record data. The minimum sample determined is 52 subjects. Univariate analysis was done using basic data characteristics of the study subjects, namely age, comorbidities, nutritional status, use of dressings, tracheal cannula replacement intervals, bacterial pattern in trachea and tracheal stoma. In this study, the comorbidities analyzed were diabetes mellitus (DM), hypertension, head and neck malignancy, history of chemotherapy, and history of radiotherapy. Analysis of bivariate data with the incidence of infection in tracheal stoma are done using the Chi-Square and Fisher tests.[8–11]

RESULTS

Results of this study showed 60 subjects met the inclusion criteria, among them, 32 subjects had tracheal stoma infections whereas 28 subjects did not have tracheal stoma infections. In tracheal and tracheal stoma swab examination, it was found that 100% were gram-negative bacteria consisting of 13 bacterial species.

a. Characteristics of subjects

Demographic characteristics in this study were age, nutritional status, comorbidities, use of dressings and interval of cannula replacement. The data is presented in a table of distribution of frequencies and percentages, based on 2 infected and uninfected groups in tracheal stoma (Table 1). Bacterial pattern with the names of bacteria described in the infected and non-infected groups in tracheal stoma. (Table 2).

In this study, 13 species of bacteria were identified, Pseudomonas aeruginosa being the microorganism mostly found, a total of 54 specimens (45%) of 120 specimens that were cultured. Pseudomonas aeruginosa was found more in tracheal stoma as much as 32 out of 120 specimens.

b. Results of Bivariate Analysis

Bivariate analysis in this study uses a comparative categorical hypothesis test using Chi-Square and Fisher. From this study, 13 species of Gram-negative bacteria were found, however due to the frequency and distribution of 9 bacterial species found were small (less

TABLE 1
Subjects' Characteristics

Variable		Tracheal Stoma Infection		Total N(%) N = 60
		Yes N (%)	No N (%)	
Age	0–5 years	0	1 (1.7%)	1 (1.7%)
	6–11 years	2 (3.3%)	0	2 (3.3%)
	12–25 years	1 (1.7%)	6 (10%)	7 (11.7%)
	26–45 years	5 (8.3%)	6 (10%)	11 (18.3%)
	46–65 years	18 (30%)	10 (16.7%)	28 (46.7%)
	>65 years	6 (10%)	5 (8.3%)	11 (18.3%)
Nutritional Status	Undernutrition	10 (16.7%)	12 (20%)	22 (36.7%)
	Good Nutrition	14 (23.3%)	13 (21.7%)	27 (45%)
	Overnutrition	8 (13.3%)	3 (5%)	11 (18.3%)
Comorbid	Yes	25 (41.7%)	16 (26.7%)	41 (68.3%)
	No	7 (11.7)	12 (20%)	19 (31.7%)
Use of dressing	*Moist dressing*	3 (5%)	3 (5%)	6 (10%)
	Sterile gauze	19 (31.7%)	21 (35%)	40 (66.7%)
	Without *dressing*	10 (16.7%)	4 (6.7%)	14 (23.3%)
Interval of cannula replacement	>30 days	28 (46.7%)	25 (41.7%)	53 (88.3%)
	<30 days	4 (6.7%)	3 (5%)	7 (11.7%)

TABLE 2
Distribution of Bacterial Pattern in Trachea and Tracheal Stoma

No	Bacterial Pattern	Trachea N (%)	Tracheal Stoma N (%)	Total N (%) N = 120
1	*Pseudomonas Aeruginosa*	22 (36.7%)	32 (53.3%)	54 (45%)
2	*Klebsiela pneumonia*	13 (21.7%)	5 (8.3%)	18 (15%)
3	*Escherichia coli*	7 (11.7%)	3 (6%)	10 (8.3%)
4	*Serratia marcescens*	3 (5%)	7 (11.7%)	10 (8.3%)
5	*Proteus mirabilis*	4 (6.7%)	2 (3.3%)	6 (5%)
6	*Acinetobacter baumannnii*	4 (6.7%)	2 (3.3%)	6 (5%)
7	*Salmonela sp*	3 (5%)	1 (1.7%)	4 (3.3%)
8	*Providencia situarti*	3 (5%)	1 (1.7%)	4 (3.3%)
9	*Enterobacter cloacae*	0	3 (5%)	3 (2.5%)
10	*Enterobakter asburiae*	1 (1.7%)	1 (1.7%)	2 (1.7%)
11	*Citrobacter koseri*	1 (1.7%)	0	1 (0.8%)
12	*Sphingomonas paucimobilis*	1 (1.7%)	0	1 (0.8%)
13	*Providencia rettgeri*	0	1 (1.7%)	1 (0.8%)
	Total	60	60	120

TABLE 3
Comparison of Trachea and Tracheal Stoma Bacterial Pattern with Tracheal Stoma Infection

Bacterial Pattern		Tracheal Stoma Infection		Total (N (%))	P value
		Yes	No		
Pseudomonas aeruginosa	Trachea	12 (22.2%)	10 (18.5%)	22 (40.7%)	0.307[a]
	Tracheal Stoma	15 (27.8%)	17 (25.9%)	32 (59.2%)	
Klebsiela pneumonia	Trachea	4 (22.2%)	9 (50%)	13 (72.2%)	0.138[a]
	Tracheal Stoma	2 (11.1%)	3 (16.7%)	5 (27.8%)	
Escherichia coli	Trachea	5 (50%)	2 (20%)	7 (70%)	1.000[b]
	Tracheal Stoma	2 (20%)	1 (10%)	3 (30%)	
Serratia marcescens	Trachea	2 (20%)	1 (10%)	3 (30%)	1.000[b]
	Tracheal Stoma	5 (50%)	2 (20%)	7 (70%)	

[a]*Chi-square pearson,* [b]*Fischer exact test*

TABLE 4
Risk Factors Analysis of Tracheal Stoma Infection

Variable		Tracheal Stoma Infection		Total N (%)	p value
		Yes N (%)	No N (%)		
Age	0–5 years	0	1 (1.7%)	1 (1.7%)	0.179[b]
	6–11 years	2 (3.3%)	0	2 (3.3%)	
	12–25 years	1 (1.7%)	6 (10%)	7 (11.7%)	
	26–45 years	5 (8,3%)	6 (10%)	11 (18.3%)	
	46–65 years	18 (30%)	10 (16.7%)	28 (46.7%)	
	>65 years	6 (10%)	5 (8.3%)	11 (18.3%)	
Nutritional Status	Undernutrition	10 (16.7%)	12 (20%)	22 (36.7%)	2.235[a]
	Good Nutrition	14 (23.3%)	13 (21.7%)	27 (45%)	
	Overnutrition	8 (13.3%)	3 (5%)	11 (18.3%)	
Comorbid	Yes	25 (41.7%)	16 (26.7%)	41 (68.3%)	1.408[a]
	No	7 (11.7)	12 (20%)	19 (31.7%)	
Use of dressing	*Moist dressing*	3 (5%)	3 (5%)	6 (10%)	0.268[b]
	Sterile gauze	19 (31.7%)	21 (35%)	40 (66.7%)	
	Without *dressing*	10 (16.7%)	4 (6.7%)	14 (23.3%)	
Interval of cannula replacement	>30 days	28 (46.7%)	25 (41.7%)	53 (88.3%)	1.000[b]
	<30 days	4 (6.7%)	3 (5%)	7 (11.7%)	

[a]Chi-square pearson, [b]Fischer exact test

than 10), the bivariate analysis could not be carried out on these species. On the other hand, the bivariate analysis that could be carried out are *Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli* and *Serratia marcescens*.[7]

Risk factors of tracheal stoma infection in this study were age, nutritional status, comorbidities, use of dressings and interval of tracheal cannula replacement.

DISCUSSION

The use of tracheal cannula resulted in the growth of bacterial colonisation of the trachea, resulting in 72% positive cultures on the 7th day after tracheostomy. Gram-negative and gram-positive bacteria can be found from tracheal swab and tracheal stoma cultures although gram-negative bacteria are more dominant, in accordance with several previous studies. In this study, overall culture results of samples showed gram-negative bacteria. Gram-negative bacteria were found more allegedly due to the ability of these bacteria to form biofilms and colonise the trachea.[2,12–14]

In this study, 13 species of bacteria were found. The results of tracheal swab culture showed most bacteria that grew were *Pseudomonas aeruginosa, Klebsiella pneumonia*, and *Escherichia coli*, meanwhile the tracheal stoma swab culture, showed most bacteria that grew were *Pseudomonas aeruginosa, Serratia marcescens* and *Klebsiela pneumonia*.

Pseudomonas aeruginosa is an opportunistic pathogen which is quite difficult to eradicate once colonised. *Pseudomonas aeruginosa* can bind to tracheal cells much more strongly so that injury to the tracheal surface due to endotracheal intubation, tracheal cannula and suctioning can also create new binding sites for *Pseudomonas*. Although most *Pseudomonas aeruginosa* was found in both trachea and tracheal stoma in this study, when bivariate analysis were carried out, showed no significant difference between the 2 groups of bacteria in the occurrence of tracheal stoma infection. Antibiotic sensitivity of *Pseudomonas aeruginosa* was reported to be sensitive to meropenem (92.6%), amikacin (94.4%), ciprofloxacin (92.6%), piperacillin/tazobactam (90.7%), cefepime (92.6%), gentamicin (96.3%), ceftazidime (92.6%), aztreonam (81.5%) and resistant to cefazolin (98.1%) and tigecycline (92.6%).[1,6,15–17]

Risk factors such as age, nutritional status, comorbidities, interval of cannula replacement and use of dressings did not affect the occurrence of tracheal stoma infection. This could happen due to lack of detailed analysis carried out on these factors, which is related to the differences in the care of the cannula in each patient.

Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter, Morganella, Providencia, Cronobacter, and *Edwardsiella* are gram-negative enteric bacilli (GNB) belonging to the *Enterobacteriaceae* family. Gram-negative enteric bacilli are a common organism causing nosocomial infections in patients with tracheal cannula. *Escherichia coli* can enter the human body through hands or appliances such as bottles, pacifiers, thermometers, and cutlery that are contaminated with faeces. *Serratia marcescens* are able to live in water, soil, leaf surfaces, in the bodies of insects, animals and humans.[1,2,10,12,16,18–20]

Limitations of this study is the usage of secondary data in the form of medical records of patients using tracheal cannula, the researcher were unable to assess the standard swab taking for each subject.

CONCLUSIONS AND SUGGESTIONS

There is no difference in bacterial pattern of the trachea and tracheal stoma on the incidence of tracheal stoma infection.

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Original Article

Pain Improvement Among Chronic Lumbar Disc Herniation Patients Underwent Epidural Triamcinolone with or without Hyaluronidase Injection within 3 Months of Follow-Up: A Prospective Study

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Abstract

Background : Chronic lumbar disc herniation (CLDH) will accompany by chronic inflammation, so the fibrosis tissues formed in the epidural space and adjacent nerve roots, and lead to mixed pain syndrome. The objectives of this study was to compare between triamcinolone only and hyaluronidase 1500 international unit (IU) administration epidural injection for treating bulged or protrusion CLDH.
Methods : This prospective study involved CLDH patients visiting the outpatient department of Neurology at Dr. Kariadi Hospital Semarang Indonesia from November 2021 until August 2022. They divided: triamcinolone (Group 1) and hyaluronidase 1500 IU and triamcinolone epidural injection (Group 2) with 3 days of hospitalization. Neurotrophic was prescribed during 3 months of follow-up and ordered for personal physical treatment. They analyzed pain improvements (NRS and Pain DETECT), and the Oswestry Disability Index (ODI) scores.
Results : The 37 subjects were recruited but 1 female dropped out cause of re-injection, so 13 males and 23 females aged between 24 to 72 years old (mean 48+2) were followed. They significantly improved (Wilcoxon test p=.000), as the NRS score was 47.9% (Group 1) and 55.4% (Group 2). ODI scores without significance (Mann-Whitney p> .005), such at 2 weeks (group 1= 20.4%, group 2= 23.6%) and 3 months (group 1= 58.1%, group 2= 53.7%). They observed nociceptive and neuropathic improvement even though needed more time for the healing process.
Conclusion : This study proved hyaluronidase administration before triamcinolone epidural injection with better improvements for treating bulged or protrusion CLDH patients.

Keywords : CLDH, nerve compression, fibrosis, pain, triamcinolone, hyaluronidase, epidural injection

INTRODUCTION

Hyaluronidase has been used for chronic inflammation diseases as its ability to inflammation mediators and inflammatory cell interaction. It can prevent many inflammatory processes such are: leukocyte attraction, vascular permeability, and edema formation. So the pro-inflammatory mediators (TNF-α, IL-1b, IL-6), IL-8, and anti-inflammatory cytokines (e.g. IL-10, TGF-b) might interfere after hyaluronidase admission. They are managed in well-regulation so able to protect injured tissues, then promote remodeling processes and re-established the healed tissues.[1] For chronic lumbar disc herniation (CLDH) patients who underwent surgeries, it could be remains of concern, as the post-surgical pain incidence on 40% to 68% even though without radicular pain syndromes find. As post-surgical epidural fibrosis formation can be reached in 20% to 36% of cases. Transforaminal or caudal epidural steroid injections might lead to pain reduction for short or moderate termed. Wherein the addition of hyaluronidase before epidural steroid and local anesthetic then followed by 25 mL normal saline presented better clinical pain improvement.[2] This fact is supported by fibrous or adhesion tissue formation inside the epidural space, so with the chance for adhering of the dura mater and nerve roots. So the tethered dura mater or nerve roots lead to chronic lower back pain.[3] Nowadays, the hypertonic saline 10% is barely applied in accordance caused by potent side effects such are: autonomic nerve system, metabolic formation, cardiac dysrhythmias, paraplegia, or the worst is dead. It can substitute with hyaluronidase 1500 unit initially, then followed by epidural steroid dan normal saline 0.9% for mechanically flushed inflammation mediators with good results.[4] Commonly the transforaminal epidural and serial caudal epidural steroid injections observed of strong for short-term and moderate for long-term reliefs among failed back surgery syndromes (FBSS) patients. The rationale used of hyaluronidase relies upon its ability to disrupt epidural adhesions might be effective for long-term pain relief, either the improvement of the lumbar spine range of motion.[5,6]

The LDH can attribute to tissue's mechanical compression at the lesion sites and accompany the sciatic pain syndrome. And approximately 76% of herniated disc patients are definite by magnetic resonance imaging (MRI) without any symptomatic complaints. Whereas the symptomatic found no correlation between the herniated volume and either severity of symptoms, neurological signs, or degree of disability. This might be explained that the chemical radiculopathy origin from inflammatory substances released due to annular tears in the disc fibrous ring playing a role in the pain present.[7] The intervertebral disc (IVD) is contained in the nucleus pulposus (NP), which is involved in immunoreactivity action when penetrating epidural space. Surrounded vascular might change its endothelial cell then lead to a permeability increase, so vasodilatation happened and the tissue's adhesion processes have been started. However the inflammatory cells may be collected and found at the herniated disc sites, such are cyclooxygenase-2 (COX-2), follistatin-like protein-1 (FSTL-1), and tumor necrosis factor-alpha (TNF-α). Administrated steroids into epidural space might give benefits for 80% to 90% to avoid surgeries for 1year of follow-up.[8]

Hyaluronidase is a water-soluble enzyme that is made of tissues rendered more permeable to fluids traveled through within. It can improve traumatic swelling, lesion site(s) edema formation, or absorption improvement.[9] This hyaluronidase is commonly administrated for treating failed back surgery syndromes (FBSS) with valuable outcomes. And by using intra epidural diluted with normal saline 0.9% then followed by steroid injections, could be separate the adhesion tissue as well as hypertonic saline. Whereas the hypertonic saline intraepidural injection can cause hypertension, dysrhythmias, or tachycardia, the opportunity of pulmonary edema, nerve disorders, increasing intracranial pressure, or event of death even though with small numbers.[10] CLDH is accompanied by common adjacent fibrosis tissues at the lesion site(s). This study is to investigate the comparison between caudal epidural steroid (triamcinolone) injection only and by adding hyaluronidase initially with a single treatment among bulged and protrusion of chronic LDH. They will be evaluated for pain improvement for a 3-month follow-up or intermediate term. Whereas commonly a 1-year follow-up underwent of epidural steroid injection might improve approximately 36% to 43% of patients.[11]

METHODS

This study is accepted for Ethical Approval by Health Research Ethics Committee RSUP Dr. Kariadi Semarang No. 1015/EC/KEPK-RSDK/2022 on 17 January 2022. The study involved CLDH with bulged and protrusion stages subjects, who were selected and collected by consecutive sampling in the outpatient Neurology department in Dr. Kariadi Hospital Semarang in Indonesia. The procedures have proceeded in the operation theater facilities under fluoroscopy guidance, and assisted by radiograph and operation room crew Subjects were prone lying on the operation table initially, then prepared for vital signs monitor with a pulse oxymeter and automatic tensimeter kit. The aseptic dropping was performed on the lower back to the sacrum area and covered by sterile clothes. The posteroanterior view will be presented of ilium and sacrum bones, also the sacral hiatus above of coccygeus or according to sacral level four in lateral view. A 3mL of lidocaine 2% was

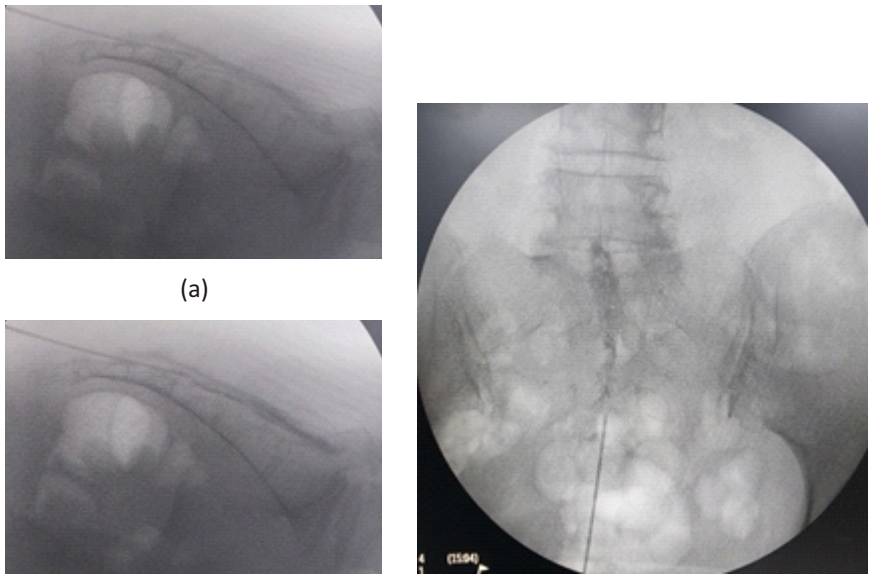

Figure 1. The caudal epidural steroid injection was performed under fluoroscopy guidance: lateral view **(a)** epidural Tuohy needle reach below of S2 vertebra level, **(b)** dye contrast injection flew within sacral epidural space, and posteroanterior view **(c)** dye contrast spreads and filling the non-compressed site (Filling Defect) likely "Christmas Tree" appearance.

injected as a local anesthetic near the entry point o the sacral hiatus, then followed by epidural Tuohy with the tip should be placed below S2 or just above S3 level. A 1 or 2 mL of Iopamiro dying contrast was injected for sure that reached into sacral and lower back epidural space. They divided into 2 groups: Group 1 as control and Group 2 with hyaluronidase interventions. Group 1 is performed of triamcinolone 40 mg/ mL in dilution with lidocaine 2% 2 mL and normal saline 0.9% 2 mL (total 5 mL), then let in 10 minutes before flushing by normal saline 0.9% 10 mL. Group 2 performed of epidural caudal injection of 1500 international unit (IU) hyaluronidase diluted in 10 mL of normal saline 0.9%, then let for 10 minutes and continued with triamcinolone 40 mg/ mL in dilution with lidocaine 2% 2 mL and normal saline 0.9% 2 mL (total 5 mL) under fluoroscopy guidance (Figure 1). The total volume of epidural injection, include with the dye contrast, is not more than 20 mL for preventing potential intracranial pressure increase. The medications were prepared by the operation nurse assistant nurse, so the agents of drugs were administrated without being recognized by the patient or the injection-performing physician. Subjects will stay for at least 30 minutes in the recovery room later for post injections observational purposes, then send back to their inpatient room department for 24 hours hospitalized. Post injections medication prescribed of levofloxacin 500 mg/ day for 4 days, and paracetamol 500 mg/ 8 hours for 5 days. While thiamine 50 mg/ 12 hours, B12/ 12 hours, and folic acid 1 mg/ 12 hours are given for 3 months as neurotrophic medications. The study is running from periods November 2021 until August 2022. This is a prospective study that analyzed pain improvement after having had analgesics prescription and conservative treatments without satisfaction.

They were followed up to determine the degree of pain relief by NRS (1-3 = mild pain, 4-6 = moderate pain, 7-10 = severe pain) and Pain DETECT (0-12 = nociceptive pain, 13-18 = mixed pain, 19-38 = neuropathic pain) scores parameter. Subjects are ordered for personal physical therapy by performing external rotation movements to the right and left in a relaxed manner in a lying position on the bed and knees flexed. This movement is performed for 30 counts and 4 cycles a day, to relax the paravertebral muscle spasm and floss the adhesion tissues inside the epidural space. This personal treatment should perform for 3 months of follow-up, so they might be in the same physical treatment applied. Failure in treatment was defined as continuous pain requiring intervention or to the extent the patient had to request additional injections or surgery.

RESULTS

Initially, this study is followed by 37 subjects CLDH, but 1 subject refused cause of her need for more analgesics prescription during 3-month followed-up. So, 36 subjects who agreed to participate are planned for intervention by 3 days hospitalized at Dr. Kariadi Hospital Semarang in Indonesia (Figure 2). They consisted of 13 males and 23 females, ages between 24 to 72 years old (mean 48±2). The pain observed reduced in both groups at 3 months

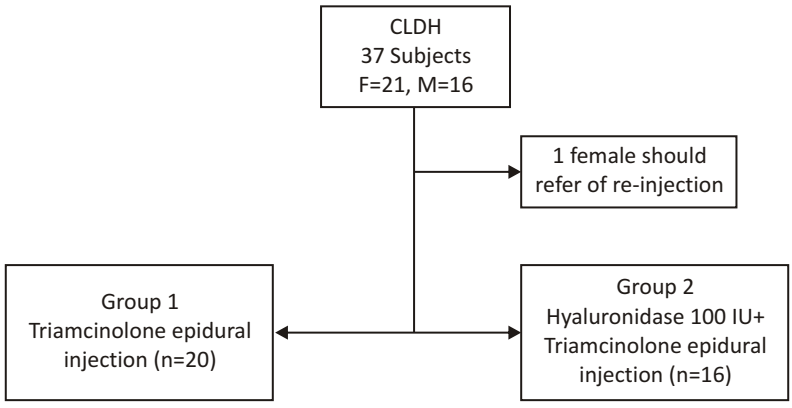

Figure 2. Subjects are recruited the study

TABLE 1
Descriptive monitoring of pain improvement in each group

Variable		Group 1		Group 2	
		(Mean±SD)	Median (Min–Max)	(Mean±SD)	Median (Min–Max)
NRS Scores	Before interventions	4.9±0.788	5 (4–6)	4.75±0.85	5 (3–6)
	at 2 weeks	3.35±0.74	3 (2–5)	3.31±0.47	3 (1–4)
	at 3 months	2.55±0.68	3 (1–4)	2.12±0.61	2 (1–3)
Pain DETECT	Before interventions	25.3±4.99	26 (14–38)	26.56±5.93	27 (18–37)
	at 2 weeks	19.25±2.91	20 (12–24)	21.81±4.26	20 (16–30)
	at 3 months	19.8±4.2	19 (12–28)	20.31±3.34	20 (14–28)
ODI	Before interventions	47.25±7.01	46 (38–68)	43.87±5.08	44 (34–54)
	at 2 weeks	38.0±6.15	38 (26–50)	33.5±4.81	24 (24–44)
	at 3 months	19.8±4.2	19 (12–28)	20.3±3.34	20 (14–28)

follow-up, as the NRS score improved by 47.9% in Group 1 and 55.4% in Group 2 (Table 1). And statistically observed with significance for both groups (Wilcoxon test, p= .000) in comparison of before and 2 weeks or 3 months of follow-up (Table 2). The pain improvement without statistical significance between Groups 1 and 2 at 2 weeks and 3 months of follow-up (p> .005) (Table 2). There was no significant differentiation of age and pain intensity improvement among both groups at 2 weeks and 3 months of follow-up (p> .005) (Table 2). Pain DETECT score is commonly used to evaluate the neuropathic pain modalities, which founds significant improvement among both groups at 2 weeks of follow-up (p< .005), and at 3 months of follow-up observed without significant (p>.005)(Table 2). Oswestry Disability Index (ODI) with improvement in both groups, as of week 2 showed a reduction of approximately 20.4% (Group 1) and 23.6% (Group 2) while at 3 months 58.1% (Group 1) and 53.7% (Group 2). But statistically without significance on both (Mann-Whitney p> .005). This study showed that subjects suffering from CLDH might observe nociceptive and neuropathic component improvement after epidural triamcinolone or epidurolysis injection.

DISCUSSIONS

Pain syndrome measurements might need detail and personalized, as pain is quite involved subjective responses. The nociceptive pain rises from inflammatory processes and might represent by NRS scores, whereas the Pain DETECT scores for evaluating the neuropathic pain involvement represent nerves injured. It seemingly represents comprehensive neuropathic pain syndromes with a sensitivity of 85% and specificity of 80%.[12,13] Both groups have shown NRS and Pain DETECT

TABLE 2
Statistical analysis

		Group 1	Group 2	All groups
NRS scores (Wilcoxon Signed Rank test)	Pre vs 2 weeks	.000*	.000*	.000*
	Pre vs 3 months	.000*	.000*	.000*
(Mann-Whitney test)	Pain improvement at 2 weeks	–	–	.694
	Pain improvement at 3 months	–	–	.422
Ages ≤50 dan >50 years	2 weeks	–	–	.888
	3 months	–	–	.355
Pain DETECT scores (Wilcoxon Signed Rank test)	Pre vs 2 weeks	.000*	.001*	.000*
	Pre vs 3 months	.005	.006	.000*
(T-test)	Pain improvement at 2 weeks	–	–	.290
	Pain improvement at 3 months	–	–	.898
Ages ≤50 dan >50 years	2 weeks	–	–	.255
	3 months	–	–	.628

*: significant results (p< .005)

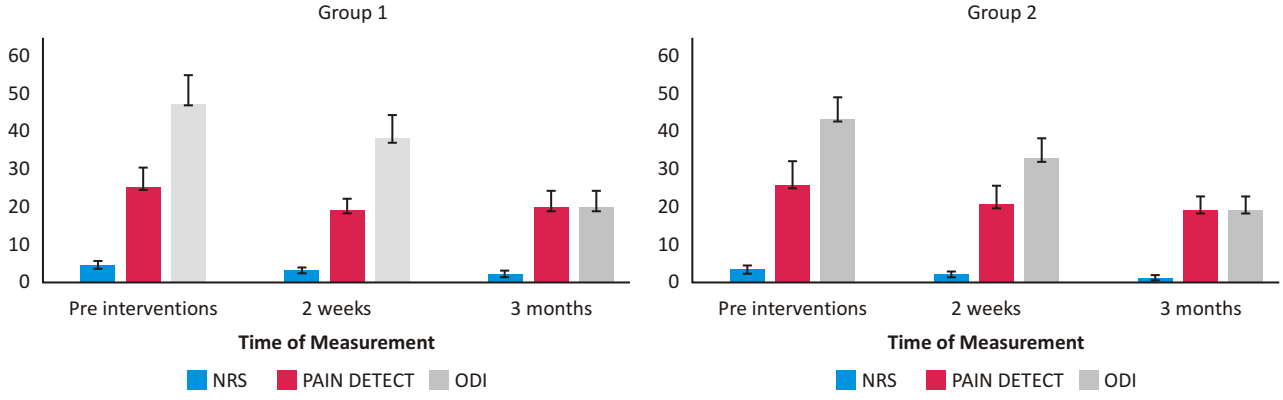

Figure 3. Pain improvement graphic of Groups 1 and 2

improvement at 2 weeks and 3 months after procedures treatment. It means the epidural steroid injection might treat both nociceptive and neuropathic pain too. A sprouted nerve founds inserted into the annular layer that leads to neuropathic pain symptoms, as the nerve ending will transmit the pain impulses to the central nerve system (CNS). It might so a common find in CLDH or degenerative disc diseases, so in this study even though leads to improvement but neuropathic pain remains. Meanwhile, a chronic state of LDH will initiate vascularisation interfered, so local ischemic tissues appeared, then anaerobic metabolism occurs. Otherwise, this hypoxic state on adjacent tissues might lead to hyperacidity environments, so the action potentials immediately appear and pain impulses are transmitted. The advanced step might present demyelination nerves that play role in neuropathic pain or radiculopathy syndromes.[7,14] An animal study of the CLBP model showed an alteration of nerve conduction velocity (NCV) which was detected by electrophysiological examination or disrupted of blood and also the cerebrospinal liquid circulation due to epidural fibrosis formation.[15,16] Intraepidural space adhesion or fibrosis formation was found in chronic LBP (CLBP) due to LDH, as in association with repetition trauma, tears on annulus fibrosis ring surface, hence leading to tethered compression at the nerve roots or adjacent structures. Herniated disc materials could be irritating on the dural sac and lesion sites around the nerve roots.[8] The herniated disc materials lead to glutamate release which induced the inflammatory response and root compression without traumatic spine experience. These alterations

might lead to gradual adhesion or fibrosis inside the epidural space, and it can be clinically examined with a dural tug maneuver. This maneuver is performed by sitting position on the bed and both legs lying down accompanied with anteriorly flexed, so can reach of toes. When the adhesion or fibrosis tissues inside the epidural space are presented, patients might feel paravertebral muscle spasms.[3,8,17] By performing the right and left external rotation movements on the bed and knees flexed, could be optimizing of the nerve roots sleeved movement. Thus the sticky tissues due to fibrosis formation can be released more, and the pain will reduce. The aging process seemed not related to the severity of the pain symptoms among CLDH patients. It is based on the degeneration process accompanied by aging accompanied by the reduction of inflammation and volume or atrophy of the disc tissues. It can cause herniated disc compression might be reduced.[18] The physical treatments addressed after epidural steroid injections or surgical might improve clinical outcomes, such are leg or radicular pain or daily activities.[19] Paravertebral structures might an essential for improving back pain, such are deep abdominal muscles, superficial muscles, transversus abdominis, and multifidus. This can improve vertebral stability in either of the pain origins. Hip muscle strengthening accompanied by lumbar stabilization could be helped with pain improvement for at least 3 weeks. The hip is frequently compensation affected while the lower back pain syndromes remain.[20]

Pain impulses might transmit going to the central nerve system (CNS) through the terminals pathway, the dorsal root ganglion (DRG) first receives pain afferent fiber of nociception. Lidocaine is a local anesthetic drug that blocked pain transmission by interfering with voltage-gated ion (Na+, K+, and Ca2+) channels. It was blocked on voltages-gate Na+or sodium channels (VGSC) then nerve excitability and potential actions reduce. Postsynaptic neurons in DRGs were influenced by K+ ion channels and the excitability might reduce when blocked by lidocaine. It also play the role in Ca2+intracellular and extracellular regulation, so the sensory and nociceptive transmission remains controlled by blocked depolarization states. Lidocaine properties can reduce spinal hyperexcitability and pain behaviors involved in chronic pain development. Meanwhile, epidural space administration could interfere with the firing of pain sensation and potential actions presented, and the DRG membrane hyperpolarized during inflammation states can be reduced.[21,22] Glutamate is the main excitatory neurotransmitter that the production of the presynaptic terminal might inhibit by lidocaine. The expression of the proinflammatory, cytokines interleukin-1b, interleukin-6, and tumor necrosis factor-α (TNF- α); might reduce after lidocaine is administrated so improving the inflammation and pain sensation. Similarly, the lidocaine administration through the epidural space might have these beneficial effects as its lipophilic agent.[21,23] Epidural steroid injection has often been applied as a therapy for LDH, either through transforaminal, interlaminar, or caudal epidural approaches even though they might relapse within 2 weeks later (35%). But others might be effective in pain improvement moderately until 2 or 9 months. The transforaminal approach could have better results than others, as approximately 25% to 57% for the long-term and 50% to 75% for a temporary duration. Around 45% to 50% of patients might feel pain recurred at 3 months later. This could be caused by a limitation of steroid action duration of around 2 to 3 weeks and can be interfered with by chronic inflammation. The fibrocyte proliferation collected collagen around the lesion site(s), or even a cicatrization around the nerve roots could be obstructed the flow of drugs.[24] All subjects with moderate disabilities regard Oswestry Disability Index (ODI) scores initially compared to post-injection. Epidural steroid injection among LDH or nerve roots compression patients commonly with post-surgical improvement following ODI scores improvement within the short or long term of 1-year follow-up.[11,25]

This study with similarities mentioned the effectiveness of pain improvement underwent epidural steroid injections at 3 and 6 months follow-up.[26] The nociceptive pain rises from inflammatory processes and might represent by NRS scores, whereas the Pain DETECT scores for evaluating the neuropathic pain states. Both groups have shown NRS and Pain DETECT improvement at 2 weeks and 3 months after procedures treatment. It means the epidural steroid injection might promote both nociceptive and neuropathic pain too. A sprouted nerve founds inserted into the annular layer that leads to neuropathic pain symptoms, as, the nerve ending will transmit the pain impulses to the central nerve system (CNS).[27] After inflammation happened will be followed by peripheral vasodilation, edema, fibrin deposition, white blood cell agglutination, and phagocytosis. Thus in a long-termed period might lead to peripheral vascular and fibroblast proliferation, the collagen collected and adhesion or fibrosis tissue formation occur at the lesion site(s). Sodium channels at the nerve roots affected might express, which facilitate pain impulses transmitted and mechanically more sensitive. The cytokine mediators accumulated around the lesion site(s) and adjacent nerve roots, then the nerve function could be easily excited by even a very weak stimulus.[9] Meanwhile, a chronic state of LDH will initiate vascularization interfered, local ischemic tissues happened, then anaerobic metabolism occurs. Otherwise, this hypoxic state on adjacent tissues might lead to hyperacidity environments, so the action potentials immediately appear and pain impulses are transmitted.[7] Fibrosis or adhesion tissue might exist at the lesion site(s) during the chronic inflammation process, so provoked

pain triggered by sticky tissue due to fibrosis inside epidural space, and will obstruct antiinflammation drugs. This study showed of the NRS score's gradual improvement was better with hyaluronidase administration or epidurolysis group at 2 weeks and 3 months post surgeries (Table 1). Even though the statistical analysis observes not significant, descriptively the improvement might be better (Figure 3). This fact might be supported the hypothesis that hyaluronidase administration with better outcomes as compared to epidural steroids alone for treating bulged and protrusion LDH. Thus with better triamcinolone flow inside the epidural space, the pain and neurofunctional improvement too. Triamcinolone with the mechanism of action antiinflammation in the long term when administration intra epidural space for managing LDH, which sprouted nerve on the annular surface so neuropathic pain present.[28] Adding 1500 IU of hyaluronidase is referred to hydrolysis mechanism on glucosamine bonds and connective tissues mucopolysaccharides. It can reduce and prevent fibrosis or scar tissue formation around. Then particularly improve the compressed os lesion site(s), nerve root sleeves moved easily within the neuroforamen, and local circulation more smoothly. Other than that steroid drugs can be spread and flow more in the epidural space.[9] It means that hyaluronidase might help optimize antiinflammation or analgesic drugs spread reach to the target site(s) better.

CONCLUSION

We realize that more numbers of the subject involved, or duration of follow-up might give good comprehensive results. This study is originally following stages 1 (bulged) or 2 (protrusion) of chronic LDH with better outcomes with hyaluronidase administration before triamcinolone epidural injection. And by the performing through of caudal epidural space also develop pain improvement. For treating chronic disc herniation, thus hyaluronidase might give a better outcome for bulged or protrusion disc herniation.

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Original Article

Difference Between BMI at Admission and Discharge and NIHSS at Admission and Discharge in Iscemic Stroke Patients at Dr. Kariadi Hospital

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Abstract

Background : Hospitalized patients are at risk for malnutrition. Decreased BMI (Body Mass Index) in stroke patients is negatively correlated with patient outcomes. Studies on differences in BMI and NIHSS (National Institutes of Health Stroke Scale) at admission and discharge in stroke patients have not been conducted in Indonesia. This study was aimed to describe the difference between BMI and NIHSS at admission and discharge in ischemic stroke patients at Dr. Kariadi hospital
Methods : An observational study on 49 hospitalized ischemic stroke patients at the Stroke Unit of dr. Kariadi hospital. Outcomes were measured using the National Institutes of Stroke Scale (NIHSS). Data was collected from the patient's medical record and analyzed using Paired Sample t Test.
Results : There was no significant difference between BMI at admission and discharge (p = 0.161). There was a significant difference between the NIHSS at the time of admission and at the time of discharge (p= 0.014).
Conclusion : There is no significant difference between BMI at admission and discharge. There is functional improvement in ischemic stroke patients during treatment.

Keywords : Stroke BMI, Stroke Outcome, NIHSS

INTRODUCTION

Patients undergoing treatment in hospitals are at risk of experiencing malnutrition. The prevalence of malnutrition in hospitalized patients ranges widely from 20% to 50%. If left untreated, this can reduce the patient's nutritional status during treatment. Of patients who were not malnourished at the time of admission, one third will experience a decrease in nutritional status during the hospitalization period.[1] Stroke patients undergoing treatment in hospital may experience malnutrition as illustrated by a decrease in body mass index (BMI). Some things that can be a risk factor for malnutrition in stroke patients include BMI at the time of admission to hospital, polypharmacy, eating difficulties, chronic diseases, functional disabilities, and high scores on the *National Institutes of Health Stroke Scale* (NIHSS).[2] In addition, decreased BMI in stroke patients can also be due to high catabolic processes due to inflammatory processes and oxidative stress conditions, as well as inadequate energy and protein intake, which is exacerbated by failure of anabolic stimulation, especially in the acute phase after stroke.[3] The NIHSS is a systematic assessment tool that quantitatively measures stroke-associated neurologic deficits. The NIHSS is a quantitative neurological assessment that includes evaluation of level of consciousness, visual field, facial expression, motor power, ataxia, language, dysarthria, and consciousness. NIHSS can be used to measure the severity and outcome of stroke patients. The NIHSS has a score ranging from 0 to 42. Higher scores are associated with increased stroke severity and a poorer prognosis.[13,14]

Malnutrition and dysphagia that occur in the acute post stroke period are associated with poor outcomes. Identification and nutrition therapy for malnutrition conditions need to be done immediately so that optimal improvement of body function can be achieved.[5,6] Proper nutrition has been shown to significantly improve the physical and mental function of stroke patients by maintaining muscle and fat mass, shortening the hospitalization period, and improving functional outcomes.[7] There is no study that compares BMI and NIHSS at admission and NIHSS at discharge in ischemic stroke patients in Indonesia. Therefore, research is needed to analyze whether there is a significant difference between BMI and NIHSS at admission and at discharge to describe the effect of proper nutrition to prevent malnutrition and improve ischemic stroke patient outcomes.

METHODS

This study uses an observational design. The data is in the form of secondary data obtained from the medical records of patients from the Stroke Unit of Dr. Kariadi Hospital for six months, from October 2021 to March 2022. Initial and final BMI data, NIHSS, length of stay, age, and gender were taken from the patient's medical records. The required number of samples is calculated using the formula:

$$n = \left[\frac{(Z\alpha + Z\beta)}{0{,}5 \ln \{(1+r)/(1-r)\}} \right]^2 + 3$$

Type I error is set at 5%, type II error is set at 20%. The minimum correlation that is considered significant (r) is set at 0.506. By using this formula, the minimum sample size required is 28. The research subjects were selected by *non-random sampling*, namely using the *consecutive sampling* of ischemic stroke patients treated at the Stroke Unit of RSUP Kariadi Semarang. The inclusion criteria were ischemic stroke patients who were hospitalized at the Stroke Unit of RSUP Dr. Kariadi, age >18 years, and complete medical record data. Exclusion criteria were patients with edema or ascites. In this study, the number of samples obtained was 49 subjects.

The variables studied were BMI at admission and at discharge and NIHSS at admission and at discharge. BMI is obtained by calculating the value of body weight at admission divided by height in the square.

Body weight is calculated using a formula based on upper arm circumference, namely:

- For male:
  Body Weight =
  Arm Circumference : 26.3 x (Height - 100)
- For female:
  Body Weight =
  Arm Circumference : 25.7 x (Height - 100)

Body height is calculated using a formula based on knee height :

- For male:
  Body Height = (2.02x Knee Height) - (0.04xAge) + 64.19
- For females:
  Body Height = (1.83xKnee Height) - (0.24xAge) + 84.88

Data was processed using a computer, with descriptive tests on nominal scale data displayed in the form of amounts (n) and percentages, data with a numerical scale are shown in the form of *mean* and standard deviation. A paired sample t test is used to determine significant difference between groups. The results of paired sample t tests are said to be significant if they meet the p value <0.05. This research has obtained *ethical clearance* from the Medical Research Ethics Commission at Diponegoro University and Dr. Kariadi General Hospital, Semarang.

RESULTS

The study was conducted on 49 Ischemic Stroke patients who were hospitalized at the Stroke Unit of RSUP Dr.

TABLE 1
Basic Characteristics of Research Subjects

Variable		F	%	Unit
Gender	Man	35	71.4	People
	Age ≥60 years	22	44.9	People
	Age <60 years	13	26.5	People
	Woman	14	28.6	People
	Age ≥60 years	12	24.5	People
	Age <60 years	2	4.1	People
Food Intake	< 60% of target	2	4.1	kcal
	60–99% of target	24	49.0	kcal
	100 % of target	23	46.9	kcal

TABLE 2
Data Description

Variable	Mean ± SD	Median (Min–Max)
Age (years)	61.2 ± 9.37	62 (26–86)
Length of treatment (days)	15.2 ± 11.26	12 (3–63)
BMI at admission (kg/m^2)	24.6 ± 4.18	25.15 (17.33–35.94)
BMI at discharge (kg/m^2)	24.4 ± 4.23	24.78 (17.33–35.94)
BMI difference (kg/m^2)	-0.2 ± 0.84	0.00 (-4.01–1.47)
NIHSS at admission	9.0 ± 4.09	8 (1–17)
NIHSS at discharge	8.3 ± 3.90	7 (1–16)
NIHSS difference	0.7 ± 1.84	0.0 (-2.0–9.0)

TABLE 3
Difference test between initial BMI and final BMI

Paired Samples Test	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1								
Initial BMI – final BMI	.17121	.84266	.12038	-.07083	.41326	1.422	48	.161
Pair 2								
NIHSS at admission – NIHSS at discharge	.673	1.842	.263	.145	1.202	2.560	48	.014

Kariadi Semarang. The characteristics of the research subjects are described in Table 1. Most of the research subjects were male, namely 71.4%, while 28.6% were female. The majority of research subjects are aged ≥60 years, namely 33 patients (67.3%). The youngest is 26 years old and the oldest is 86 years. The majority of research subjects received food intake ≥60% of target. Twenty-four research subjects received food intake ≥60% of target and 23 research subjects had achieved 100% food intake as targetted. Only two research subjects had not reached 60% of target.

A description of the research data can be seen in Table 2. The minimum length of stay is 3 days, the maximum is 63 days, and the average is 15.2 days. Both BMI at admission and discharge have a minimum value of 17.33 kg/m^2 and a maximum of 35.94 kg/m. The difference in BMI during treatment averaged -0.2 kg/m^2 with an SD of 0.84. Test results of Paired Sample t Test showed no significant difference between BMI at admission and BMI at discharge (t=1.422, p= 0.161). NIHSS at admission averaged 9.0 and NIHSS at discharge averaged 8.3. Test results Paired Sample t Test showed a significant difference between NIHSS at admission and NIHSS at discharge (t=2.560, p=0.014).

DISCUSSION

Stroke is a functional disorder of the brain that occurs suddenly due to impaired blood circulation in the brain.[8] Stroke is one of the leading causes of morbidity and mortality in various countries.[9,10] The Indonesian Ministry of Health in 2013 stated that stroke is the number one cause of death and disability in Indonesia. The prevalence of stroke in Indonesia is 7 per 1000 population.[11] Stroke patients who are hospitalized can experience malnutrition as illustrated by the decrease in body mass index (BMI). Research by Dewi found that more stroke patients are malnourished than those who are not.[12] The causes of malnutrition in stroke patients include paralysis and neurological deficits.[13] The decrease in BMI in stroke patients can also be caused by a high level of catabolism. The high catabolism in stroke patients is caused by inflammatory processes and oxidative stress conditions, inadequate energy and protein intake, and exacerbated by anabolic failure, especially in the acute phase after stroke.[14] Subarachnoid hemorrhage (SAH) causes an increase resting energy expenditure (REE) which is higher than ischemic stroke and intracerebral hemorrhage (ICH).[2] Outcomes of stroke patients can be measured using National Institutes of Health Stroke Scale (NIHSS).[15]

Several things that can be risk factors for malnutrition in stroke patients include BMI at hospital admission, polypharmacy, eating difficulties, comorbid diseases, functional disabilities, and high score of National Institutes of Health Stroke Scale (NIHSS) which is high.[2] Neurological deficits such as decreased visual function, weakness of the upper limbs, and decreased intake can trigger depression and apraxia which affect patient's ability to eat, thereby increasing the risk of malnutrition.[6] Weight loss after stroke can be caused by a negative energy balance caused by a deficit in caloric intake and the inflammatory condition experienced by the patient, which in turn can lead to an increase in sarcopenia that occurs due to paresis and a decrease in physical activity. Catabolic-anabolic imbalance can be further exacerbated by increased catabolic drive and failure of anabolic stimulation.[15] Weight loss in stroke patients has a negative correlation with patient outcomes and the return of physical function in the long term, so it is important to prevent this decrease in muscle mass.[16,17] Approximately 40% of stroke patients in rehabilitation centers, especially stroke patients with dysphagia are at risk for suffering from malnutrition during the treatment process.[18] Malnutrition in stroke patients has a negative impact on patient outcomes. This is because at the cellular level, the protein and energy deficiencies that occur when a patient is admitted to the hospital can interfere with the recovery of hippocampal fibers in ischemic brain injury by changing the expression of trkB and the GAP-43 protein.[2] Stroke patients with malnutrition have a higher mortality rate (37%) than stroke patients with normal nutritional status (21%).[19]

It is known that in the acute phase of stroke, oxidative stress occurs which suppresses protein synthesis resulting in disruption in brain recovery. Proper nutrition since that phase has been proven to significantly improve the physical and mental function of stroke patients by maintaining muscle and fat mass, shortening the hospitalization period, and improving functional outcomes.[7]

This study assessed differences in BMI at admission and BMI at discharge as well as NIHSS at admission and NIHSS at discharge in stroke patients who were hospitalized at the Stroke Unit of RSUP Dr. Kariadi Semarang. All ischemic stroke patients who are hospitalized in the Stroke Unit of Dr. Kariadi received integrated treatment between medical therapy and medical nutrition therapy by a clinical nutrition specialist immediately from the time the patient was admitted, thus allowing to decrease the level of inflammation and the risk of catabolism. This is reflected in the distribution of research data which shows that the majority of research subjects (95.9%) received intake ≥ 60% of the target with 23 research subjects (46.9%) having achieved intake of 100% of the target. This study showed that there was no significant difference between BMI at admission and discharge (t=1.422, p = 0.161). The result of Paired Sample t Test showed a significant difference between NIHSS at admission and NIHSS at discharge (t=2.560, p=0.014). NIHSS at discharge showed improvement compared to NIHSS at admission which illustrates an improvement in

the outcome of ischemic stroke patients undergoing hospitalization at the Stroke Unit of RSUP Dr. Kariadi Semarang. The significant improvement of NIHSS accompanied by no significant decrease in BMI in ischemic stroke patients who were hospitalized at the Stroke Unit of Dr. Kariadi Hospital Semarang demonstrated the role of medical nutrition therapy along with integrated medical therapy so as to minimize weight loss in acute phase ischemic stroke patients and improve patient outcomes. This is in line with the study of Aquilani *et al.* which said that providing proper nutrition since the acute phase of stroke is proven to significantly improve the physical and mental function of stroke patients by maintaining muscle and fat mass, shortening the hospitalization period, and improving functional outcomes.[7] This is also in line with the research of Nii M *et al.* who said that nutritional therapy while in hospital is related to functional improvement in stroke patients.[20]

CONCLUSION

There was no significant difference between BMI at admission and BMI at discharge which indicated that the patient's weight during treatment tended to be stable. There was a significant difference between the NIHSS at admission and at discharge which showed an improvement in outcomes during hospitalization. This shows the role of medical nutrition therapy together with integrated medical therapy in minimizing weight loss and improving patient outcomes in acute phase ischemic stroke patients who were hospitalized at the Stroke Unit of Dr. Kariadi Hospital Semarang.

The limitation of this study is the exclusion of various factors that influence the outcome of ischemic stroke patients, namely age,function and physical disabilitypra-stroke, severity of initial symptoms, education, diabetes mellitus, and baseline CT scan. Further research is necessary using more specific nutritional status assessment parameters such as body composition examination in order to obtain more detailed data.

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Original Article

Potential of Hibiscus *(Hibiscus rosa sinensis L.)* Ethanol Extract as Root Canal Medicament Materials

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Abstract

Background : Enterococcus faecalis is the dominant bacteria found in root canals, especially in failure of root canal treatment. Therefore, antibacterial agents are required as a means to achieve complete disinfection of the root canal system. One of the natural ingredients that has been proven to have antibacterial properties is the ethanol extract of hibiscus *(H. rosa sinensis L.)*, so it has the potential to be used as a root canal medicament to inhibit growth and eliminate E. faecalis bacteria. This study was aimed to test the effectiveness of hibiscus *(H. rosa sinensis L.)* ethanol extract as a potential root canal medicament.
Methods : The study was conducted using a true experimental post-test only control group design in 6 treatment groups with various concentrations of hibiscus extract (100%, 50%, 25%, 12.5%, 6.25, and 3.125%) and a positive control group. (Brain Heart Infusion added *E. faecalis*) and negative (Brain Heart Infusion). The extract was then diluted to the concentration used and added with 1.5x108CFU/ml *E. faecalis* and then cultured using the spread method on NA media, incubated anaerobically at 37oC for 24 hours, then the colonies that grew were counted using a colony counter.
Results : The results showed that 100% concentration had the highest ability to inhibit the growth of E. faecalis bacteria (92.7%) with an average number of colonies growing of 4.4 x 102 CFU/ml. The minimum inhibitory concentration (MIC) was shown at a concentration of 50%, with an inhibiting ability of 90.17% and the average number of colonies that grew was 5.9 x103 CFU/ml. Kruskal Wallis statistical test showed a significant difference in the number of colonies ($p<0.05$).
Conclusion : Hibiscus extract with a concentration of 100% has the highest ability to inhibit the growth of E. faecalis bacteria and MIC is present at a concentration of 50%.

Keywords : *H. rosa sinensis L., E. faecalis*, root canal medicaments, MIC, inhibition ability

INTRODUCTION

People are starting to understand that treating aching teeth is a good idea to prevent tooth decay and even tooth loss.[1] The endodontic triad consists of preparation, shaping and cleaning of the root canals, as well as obturation or filling of the root canals which are the keys to successful endodontic treatment.[2] Endodontic treatment aims to maintain the tooth in the oral cavity as long as possible by filling the root canal and forming a good closure at the apical foramen of the tooth so that it cannot be penetrated by infectious fluids secondary to leakage of the periradicular tissue.[3] Endodontically treated teeth should be evaluated clinically and radiographically to ensure that the root canal treatment was considered successful and that the tooth is functional.[4]

Failure of endodontic treatment can be determined based on clinical and radiographic signs and symptoms found in teeth that have been treated with root canals.[5] Common factors leading to failure of endodontic treatment are inadequate root canal filling, filling leaks, untreated root canals, iatrogenic procedure errors, instrumentation complications such as perforation and persistence of bacteria in the root canal area such as isthmus, dentinal tubules, and bifurcation.[4] *E.faecalis* is a gram-positive bacterium which results in 70% of cases of canal treatment failure because it is able to invade, settle in the dentinal tubules and is resistant to antibacterials so that it can survive in the root canals in an alkaline pH environment.[6–9]

Calcium hydroxide is a root canal drug that is commonly used because it has antibacterial properties that work by diffusion from OH^- ions so that the pH is alkaline and does not support the environment for anaerobic bacteria in the root canals.[9–11] Calcium hydroxide has low solubility and diffusibility, so it cannot kill bacteria located in the isthmus, dentinal tubules, and bifurcations especially in *E. faecalis* and has a negative impact on periodontal tissue and is difficult to clean from the root canal walls.[12,13]

Alternative root canal drugs are needed to inhibit the growth of *E. faecalis*, so that the bacteria does not develop and cause secondary infections in the root canals. Root canal medications that are commonly used contain many synthetic chemicals that will have a negative impact, while herbal products are increasingly popular. Research in this regard continues to be carried out to find basic ingredients from traditional plants and materials that are non-toxic, biocompatible, and easily available in Indonesia's natural environment, which are expected to be used as substitutes for synthetic chemicals.[14]

Natural ingredients that are believed to have antibacterial properties are hibiscus *(Hibiscus rosa sinensis L.)*.[15] The results of phytochemical screening in previous studies stated that hibiscus leaf and flower extracts contain chemical compounds that play a role in inhibiting the growth of *E. faecalis* bacteria because they have active ingredients such as flavonoids and phenols which have significant inhibitory power.[16] Flavonoids can lyse bacteria because they have the ability to disrupt the integrity of cell membranes so that they can reduce the physiological activity of bacteria, while phenols work by damaging cell membranes and enzymes in bacteria. Another study found that high concentrations of the methanol extract of the hibiscus plant *(H. rosa sinensis L.)* showed strong activity against *Streptococcus mutans*.[17,18]

Based on the description above, it is known that hibiscus *(H. rosa sinensis L.)* has potential as a root canal medicament. In addition, hibiscus is also biocompatible with low toxicity, but no studies have tested the effectiveness of this plant against *E. faecalis* in root canals.[19] Therefore, researchers feel the need to conduct research on the antibacterial power of hibiscus *(H. rosa sinensis L.)* ethanol extract on the growth of *E. faecalis*, considering that this plant has the potential as a root canal medicament.

METHODS

The research was carried out at the Microbiology Laboratory of the Faculty of Medicine and the Diponegoro University Semarang Integrated Laboratory from October to December 2020. A true experimental study with a post-test only control group design was used as the type of study. The materials used in this study included ethanol extract of hibiscus *(H. rosa sinensis L.)* with the specified concentrations of 100%, 50%, 25%, 12.5%, 6.25%, and 3.125% and the control group was a positive control containing BHIB *(Brain Heart Infusion Broth)* media with the addition of *E. faecalis* bacteria which had been adjusted to the Mc Farland 0.5 standard and the negative control only containing BHIB media. The *E. faecalis* bacteria is the result of culture from the Diponegoro University Microbiology Laboratory.

Hibiscus *(H. rosa sinensis L.)* obtained from the yard of the Faculty of Public Health UNDIP was then aerated until it reached a moisture content of <20% and extracted by maceration method using 70% ethanol solvent. The ethanol extract of hibiscus *(H. rosa sinensis L.)* with honey-like consistency was diluted (dilution) and various concentrations were obtained as the treatment group. *E. faecalis* seeding as much as 0.05 ml which had been standardized with Mc Farland 0.5 (1.5 × 108CFU/ml) was then added to the tube of the treatment and positive control groups, then labeled according to the concentration and incubated anaerobically at 37°C for 24 hours. Changes in turbidity in the treatment group were observed by comparison with the control group. Each tube in the treatment and control groups was taken 0.1 ml with a micropipette and planted in Nutrient Agar (NA) media using the spreading technique, then incubated

anaerobically at 37°C for 24 hours. The counting of growing colonies was then carried out using a colony counter and expressed as colony forming units (CFU/ml). Calculation of the number of sample replications refers to the Federer formula, so that it is obtained that each treatment group was replicated 4 times.

RESULTS

The data obtained in this study were primary data, namely the number of *E. faecalis* colonies that grew on NA media. Colonial growth of *E. faecalis* after incubation occurred in all treatment groups and positive control. The results of counting the number of colonies can be seen in Table 1.

Table 1 shows that the concentration of 100% has the smallest average number of colonies, namely 4.4 x102 CFU/ml, whereas at concentrations of 25% to 3.125% the average number of colonies Too Numerous To Count (TNTC) because it has > 300 colonies.

Calculation of MIC and MBC determination:
Concentration 100% =

$$\frac{44}{600} \times 100 = 7{,}3\% \longrightarrow 100\% - 7{,}3\% = 92{,}7\%$$

Concentration 50% =

$$\frac{59}{600} \times 100 = 9{,}83\% \longrightarrow 100\% - 9{,}83\% = 90{,}17\%$$

The Minimum Inhibitory Concentration (MIC) in this study was conducted to identify the antibacterial activity of the ethanol extract of hibiscus *(H. rosa sinensis L.)*. MIC is the smallest concentration of the experimental substance that can kill 90% of the bacteria from the average number of growing bacterial colonies. This study resulted in the average number of *E. faecalis* colonies growing at a concentration of 100% which was 4.4 x102 CFU/ml, while at a concentration of 50% it was 5.9 x103 CFU/ml. Based on these results, it is known that a concentration of 100% has the ability to inhibit the growth of *E. faecalis* by 92.7%, and a concentration of 50% has the

TABLE 1
The results of the descriptive analysis of counting the number of E. faecalis colonies

	Number of Bacterial Colonies (CFU/ml)							
Replication	**100%**	**50%**	**25%**	**12.5%**	**6.25%**	**3.125%**	**K+**	**K-**
1	$1x10^2$	$1.4x10^3$	TNTC	TNTC	TNTC	TNTC	TNTC	0
2	$3.6\ x10^2$	$5.1x10^3$	TNTC	TNTC	TNTC	TNTC	TNTC	0
3	$4.2\ x10^2$	$6.4\ x10^3$	TNTC	TNTC	TNTC	TNTC	TNTC	0
4	$5.4\ x10^2$	$6.2\ x10^3$	TNTC	TNTC	TNTC	TNTC	TNTC	0
Mean	$4.4\ x10^2$	$5.9\ x10^3$	TNTC	TNTC	TNTC	TNTC	TNTC	0

K+ = Positive control
K- = Negative control
TNTC = Too Numerous To Count.[20]

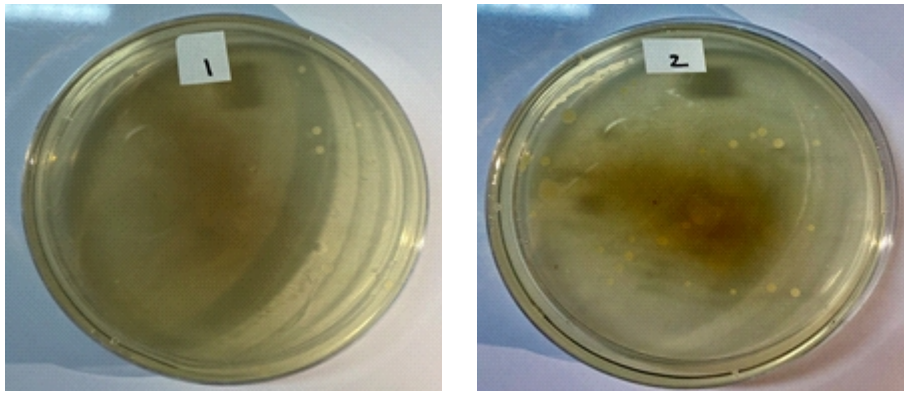

Figure 1. Colony growth of *E. faecalis* on NA media after 24 hours of incubation. (1) *E. faecalis* colony growth at 100% concentration; (2) Colony growth of *E. faecalis* at 50% concentration.

TABLE 2
The results of the Kruskall Wallis test for antibacterial activity of the ethanol extract of hibiscus *(H. rosa sinensis L.)*

Replication	Group	Mean Rank	p Value
Antibacterial power of ethanol extract of hibiscus *(H. rosa sinensis L.)*	100%	7.50	0.000*
	50%	9.50	
	25%	14.50	
	12.5%	18.50	
	6.25%	22.75	
	3.125%	26.25	
	K+	30.50	
	K-	2.50	

*Significant p<0.05

TABLE 3
Mann Whitney post hoc test results

	Group							
Group	**100%**	**50%**	**25%**	**12.5%**	**6.25%**	**3.125%**	**K+**	**K-**
100%	–	0.248	0.021*	0.021*	0.021*	0.021*	0.014*	0.014*
50%	0.248	–	0.021*	0.021*	0.021*	0.021*	0.014*	0.014*
25%	0.021*	0.021*	–	0.021*	0.021*	0.021*	0.014*	0.014*
12.5%	0.021*	0.021*	0.021*	–	0.021*	0.021*	0.014*	0.014*
6.25%	0.021*	0.021*	0.021*	0.021*	–	0.043*	0.014*	0.014*
3.125%	0.021*	0.021*	0.021*	0.021*	0.043*	–	0.014*	0.014*
K+	0.014*	0.014*	0.014*	0.014*	0.014*	0.014*	–	0.008*
K-	0.014*	0.014*	0.014*	0.014*	0.014*	0.014*	0.008*	–

*Significant p<0.05

ability to inhibit the growth of *E. faecalis* by 90.17%. Therefore, the concentration of 50% is determined as the MIC.

In addition to MIC, in order to identify the antibacterial power of the ethanol extract of hibiscus *(H. rosa sinensis L.)* can also be done by determining the Minimum Bactericidal Concentration (MBC). MBC is the smallest concentration of experimental material that can kill 99.9% of bacteria from the average number of bacterial colonies that have successfully grown. In this study, all test concentrations (100%, 50%, 25%, 12.5%, 6.25%, and 3.125%) still contained *E. faecalis* colony growth, so it can be said that the MBC could not be determined.

The results of the normality test carried out using Shapiro Wilk are intended to see the distribution of the data, and the data is categorized as normal if the p value is >0.05. In this study the significance values for concentrations of 100%, 50%, 25%, 12.5%, 6.25%, and 3.125% respectively were 0.671; 0.122; 0.415; 0.360; 0.662; and 0.830. These results indicated that overall the data on the growth of the number of colonies of *E. faecalis* at all concentrations of the treatment groups had normal distribution data. Homogeneity test with Levenne's test obtains a significance value of 0.004 ($p > 0.05$), so it can be said that the data is not homogeneous. Therefore, in order to determine the antibacterial power of the ethanol extract of hibiscus *(H. rosa sinensis L.)* against *E. faecalis*, a

non-parametric Kruskall Wallis test was carried out and followed by the Mann Whitney post hoc test with a significant value of p<0.05.

The results of the Kruskal Wallis test in Table 2 showed that there was a significant difference in the number of *E. faecalis* colonies in the eight treatment groups (p <0.05), so that it was continued with the Mann Whitnney Post Hoc test to find out the differences between groups.

Table 3 shows that the concentrations of 100% and 50% have a p>0.05, which means that there is no significant difference in the number of *E. faecalis* colonies in the two groups. However, at concentrations of 25%, 12.5%, 6.25%, 3.125%, the positive control and negative control had p <0.05 which means there was a significant difference in the number of *E. faecalis* colonies.

DISCUSSION

The aim of this study was to determine the potency of hibiscus *(H. rosa sinensis L.)* ethanol extract as a root canal medicament, which showed a significant difference in the number of *E. faecalis* colonies (p<0.05). The results showed that the greater the concentration of the ethanol extract of hibiscus *(H. rosa sinensis L.)* the lower the average growth of *E. faecalis*. This happened because the greater the concentration of the ethanol extract of hibiscus *(H. rosa sinensis L.)* used, the greater the chemical compounds contained in the plant extract. The chemical compounds contained in the ethanol extract of hibiscus *(H. rosa sinensis L.)* are flavonoids, tannins, saponins, and terpenoids which are polar. These chemical compounds are secondary metabolites which are proven to have antibacterial properties and can be used to inhibit the growth and kill bacteria.[22]

The polar chemical compounds were extracted by maceration using 70% ethanol which was also polar. The use of this solvent is because polar solvents have the ability to bind and attract/dissolve polar and nonpolar chemical compounds contained in an extracted material better than nonpolar solvents which will only bind and attract/dissolve nonpolar compounds only.[23] Therefore, its use as a solvent is considered the best to be able to attract compounds in hibiscus *(H. rosa sinensis L.)* which have the potential as an antibacterial to inhibit the growth or kill *E. faecalis* bacteria.

E. faecalis has virulence factors that cause this bacterium to survive and have the ability to form colonization.[24] Extracellular surface protein (ESP) is a virulence factor that protects these bacteria from environmental stresses such as changes in pH, osmotic changes, and temperature. This ESP also plays a role in the exchange of ions such as cations, metals, and toxins. Chemical compounds that are positively charged will interact with the negatively charged *E. faecalis* so that the outer cell membrane is damaged and causes bacterial constituents to come out. However, the positive charge of these chemical compounds can be inhibited by the negatively charged ESP so that the bacteria can inactivate the antibacterial.[25,26]

Antibacterials are chemical compounds that have the property of lysing or inhibiting the growth of pathogenic bacteria with low toxicity to humans.[27] Pelczar and Chan (2008) suggested that the mechanism of action of antibacterials can be divided into bacteriostatic and bactericidal. Bacteriostatic is a chemical compound that can inhibit or suppress the growth of bacteria, while bactericidal is a chemical compound that can kill bacteria.[28] The results of the MIC and MBC tests using the dilution method showed that the ethanol extract of hibiscus *(H. rosa sinensis L.)* could only inhibit the growth of *E. faecalis*. This means that in this study, the extract was bacteriostatic, with an inhibitory power on the growth of *E. faecalis* bacterial colonies of 92.7% at an extract concentration of 100%, while a concentration of 50% had the smallest inhibition, namely 90.17%, so that this concentration can be said to be the MIC.

The results of the research that has been carried out are in line with research by Pangkuan *et al*., (2020) which revealed that hibiscus flower extract contains a relatively weak inhibitory effect on the growth of *Streptococcus mutans* bacteria.[17] Goering *et al*., (2013) suggested that bacteriostatic is an antibacterial property that can inhibit bacterial growth and is temporary (reversible). The bacteriostatic nature has a mechanism of action by inhibiting protein synthesis which temporarily binds to the ribosome of an organism. The bond of the organism's ribosomes can be released when its concentration and stability decrease, so that the antibacterial agent will release the ribosome again and cause the bacteria to grow again.[22] Chemical compounds lyse bacterial cells because they can damage the integrity of the bacterial cell membrane, causing bacterial cell lysis. Tannin compounds are able to inhibit bacterial growth by inhibiting enzyme production, interfering with enzymatic reactions and reducing calcium ions which have a role in the plasma coagulation process. Flavonoid compounds found in hibiscus flowers are antibacterial because they contain phenol groups which break down proteins and damage cell membranes thereby inhibiting bacterial growth. That is why the chemical compounds from the ethanol extract of hibiscus *(H. rosa sinensis L.)* can inhibit and suppress the growth of *E. faecalis* bacteria. However, it is still necessary to carry out toxicity tests and stability tests of the ethanol extract of hibiscus *(H. rosa sinensis L.)* in relation to its use as a root canal medicament.

CONCLUSION

The inhibition of the growth of *E. faecalis* bacterial colonies at a concentration of 100% ethanol extract of hibiscus *(H.*

rosa sinensis L.) was 92.7%, while a concentration of 50% had the smallest inhibition, namely 90.17%, so this concentration could be said to be the MIC. Therefore, this hibiscus ethanol extract has the potential to be used as a root canal medicament.

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Original Article

Analysis of Genetic Variation of Angiotensinogen M235T Gene in Ischemic Stroke Patients treated at Dr. Kariadi General Hospital, Semarang using Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) Method

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Abstract

Background : Stroke is the leading cause of death and disability in the world. The incidence of ischemic stroke is influenced by genetic factors, environmental factors and their interactions. Genetic variation of the Angiotensinogen (AGT) M235T gene is associated with hypertension and diabetes mellitus, which are risk factors for stroke. The objectives of this study was to examine the genetic variation of the Angiotensinogen M235T gene in patients with Ischemic Stroke treated at Dr. Kariadi General hospital, Semarang.
Methods : The subjects of the study were 72 ischemic stroke patients who were treated at the outpatient clinic of the Neurology Department Dr. Kariadi Semarang in January – December 2013. DNA extraction of research subjects was performed at the CEBIOR laboratory, Diponegoro National Hospital from January to March 2020. Amplification was performed with Polymerase Chain Reaction (PCR). Digestion of PCR products was using Restriction Fragment Length Polymorphism (RFLP) method.
Results : Out of 72 samples, the AGT M235T CT were found in 37 samples (51.4%), the AGT M235T TT gene was found in 35 samples (48.6%) and no samples showed the AGT M235T CC.
Conclusion : There are 3 types of genetic variants of the AGT M235T gene, including the AGT M235T CT, the AGT M235T TT and the AGT M235T CC. Among the three types of variants, the variant of the AGT M235T CT gene is the most common variant found in ischemic stroke patients treated at the Dr. Kariadi General Hospital Semarang.

Keywords : AGT M235T, Angiotensinogen, hypertension, ischemic stroke

INTRODUCTION

Stroke is the main cause of morbidity and mortality in the world.[1,2] There was around 25,7 juta million stroke cases in the world in 2013, which approximately 80% of stroke cases are ischemic strokes. Ischemic stroke is a multifactorial disease with a strong genetic component.[2,3] Ischemic stroke is influenced by genetic factors, environmental factors and the interaction of both factors.[1]

Data from various studies conducted mostly on Caucasian ethnicity showed that there were 23 variants of the AGT gene that had been cloned and sequenced, genetic variations were found in the promoter (g.-217G> A, g.-20A> C, g.-6G> A) and in exon 2 (p.T174M and M235T) which are reported to be associated with essential hypertension and cardiovascular disease and stroke. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) is a technique for analyzing DNA fragments using restriction enzymes with endonucleases.[4–6]

The lack of data regarding the genetic contribution of patients with cardiovascular disease such as ischemic stroke in Asian populations, especially Indonesia, has encouraged researchers to identify the genetic variant of angiotensinogen in post-ischemic stroke patients. Angiotensinogen was chosen because in various studies it was stated that angiotensinogen is associated with hypertension and diabetes mellitus which are risk factors for stroke.

MATERIALS AND METHODS

The sample in this study was DNA storage from 72 subjects of a study entitled "Pengaruh Faktor Risiko terhadap Progresivitas Aterosklerosis Penderita Pasca Stroke Non Hemoragik" (main researcher: Dr. dr. Dodik Tugasworo, Sp.S(K)) at the outpatient clinic of the Neurology Department of Dr. Kariadi General Hospital Semarang in January – December 2013". The study subjects had inclusion criteria including acute ischemic stroke patients for the first time, 48 hours of stroke onset which had been proven by head CT scan without contrast and willing to participate in the study. Exclusion criteria for the subjects of this study included patients with haemorrhagic stroke, as evidenced by a non-contrast CT scan of the head; patients with severe systemic diseases, including: Chronic Kidney Disease, as evidenced by measuring the Glomerular Filtration Rate (GFR) and examination of serum urea and creatinine, chronic liver disease, proven by laboratory tests of liver function (such as: SGOT, SGPT, Gamma GT, and Alkali Phosphatase), malignancy, proven by a complete history of malignancy in the patient and family and physical examination, Congestive Heart Failure, proven by physical examination and examination electrocardiography; acute ischemic stroke patients who died or were discharged before the 7th day of onset; acute ischemic stroke patients who died before the 14th day of onset; patients died; and patients withdrew.

Analysis of genetic variation

Analysis of genetic variation of the AGT M235T gene by PCR-RFLP was carried out from January to March 2020 at the CEBIOR Laboratory, Diponegoro National Hospital. Amplification with Polymerase Chain Reaction was carried out using a Forward primer with a DNA sequence of 5'-CAGGGTGCTGTCCACACTGGACCCC-3' and Reverse with a DNA sequence of 5'-CCGTTTGTGCAGGGCCTGGCTCTCT-3'. The total volume of each PCR reaction was 24 µl containing 400 ng of genomic DNA, 1.0 µl of primer F (Sigma, city, country), 1.0 µl of primer R (Sigma), 1.0 µl of deoxynucleotide triphosphates (dNTP), 2.5 µl of MgCl2 and 0.25 µl of Taq DNA polymerase (MRC Holland lot.D56). The PCR reaction was carried out using a thermocycler with the program: initial duplex DNA denaturation 10 minutes at 95°C, followed by 35 cycles consisting of: 1 minute denaturation at 94°C, 1 minute primers annealing at 59°C and 1 minute 30 seconds primers extension at 72°C. Final elongation for 10 minutes at 72°C.

AGT M235T gene variant was detected by Restriction Fragment Length Polymorphism (RFLP) technique using restriction endonuclease Tth111I enzyme. Product PCR was carried out in a 100 µl reaction mixture and contained: 85 µl H2O, 10 µl buffer and 5U Tth111I. The restriction mixture was ingested for >3 hours at 55°C (37°C overnight). DNA fragments were visualized in 3% Agarose gel stained with 8µl 10mg/mlethidium bromide. For normal (wild type) genotype (CC) is a PCR product at 165bp, with no truncation site for Tth111I. M235T homozygous subject (TT genotype) after enzymatic destruction with Tth111I on two fragments of 141 bp and 24 bp. Heterozygous subjects (CT genotype) at 165 bp, 141 bp and 24 bp.

RESULTS

In this study, the number of samples analyzed was 72 samples from 72 subjects who had completed all research procedures in the preliminary study. The mean age of the subjects was 61.64 ± 7.995 years, most of the subjects were male (61.1%). The average BMI of the study subjects was normal, 22.27 ± 2.138 kg/m^2 (Table 1).

The results of the analysis of genetic variation of the AGT M235T gene by PCR-RFLP showed that the AGT M235T CT gene variant was the most variant, 37 (51.4%) samples, while the AGT M235T TT variant was found in 35 (48.6%). In this study, there were no samples showing AGT M235T CC variants (Table 2).

TABLE 1
Subject characteristics

Variable (n=72)		F	%	Mean±SD
Age (year)	1–60	30	41.7	61.64 ± 7.995
	>60	42	58.3	
Gender	Male	44	61.1	
	Female	28	38.9	
BMI (kg/m^2)				22.27 ± 2.138
Smoking history	Yes	31	43.1	
	No	41	56.9	
Diabetes Mellitus	Yes	6	8.3	
	No	66	91.7	
Dyslipidemia	Yes	62	86.1	24 (33.3%)
	No	10	13.9	
Obesity	Yes	10	13.9	
	No	62	86.1	
Hypertension	Yes	24	33.3	
	No	48	66.7	

TABLE 2
Subject characteristic based on gene variant AGT M235T

Variable (n=72)	Gene variant AGT M235T		
	CC	CT	TT
Gene variant AGT M235T(%)	0	51.4	48.6
Age (year)	0	60.54±8.27	62.80±7.63
Gender, male (%)	0	26.38	34.72
BMI (kg/m^2)	0	22.25±2.20	22.30±2.09
Smoking history (%)	0	19.44	23.61
Diabetes Mellitus (%)	0	4.16	4.16
Dyslipidemia (%)	0	43.05	43.05
Obesity (%)	0	6.94	6.94
Hypertension (%)	0	20.83	12.5

DISCUSSION

The human AGT gene is a member of the serpin gene superfamily. The human AGT Complimentary DNA (cDNA) is 1,455 nucleotides long and codes for 485 amino acids in proteins. The AGT gene contains five exons and four introns, spanning 13 kb (Figure 1).[7,8]

The AGT gene provides instructions for making a protein called angiotensinogen. This protein is part of the renin-angiotensin system, which regulates blood pressure and the balance of fluids and salts in the body. In the first step of the blood pressure regulation process, angiotensinogen is converted to angiotensin I. Through an additional step, angiotensin I is converted to

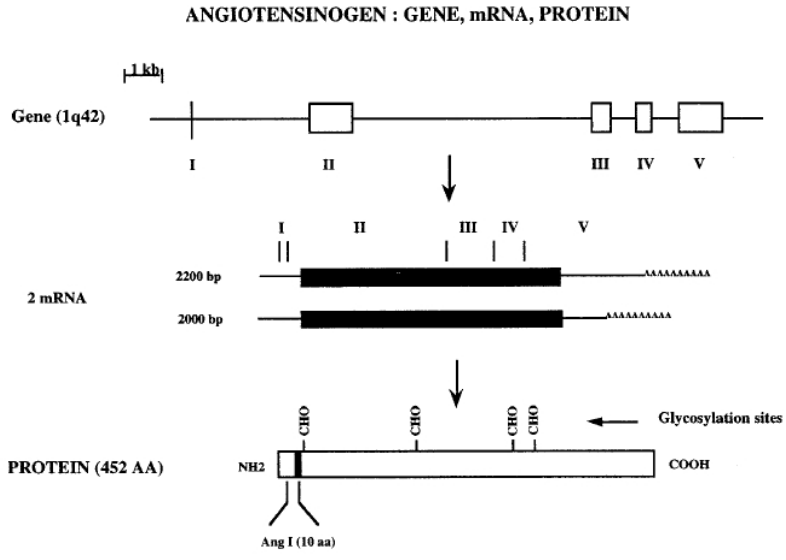

Figure 1. Schematic structure of AGT gene, mRNA, and protein[9]

angiotensin II. Angiotensin II causes blood vessels to narrow (constrict), which results in an increase in blood pressure. Angiotensin II also stimulates the production of the hormone aldosterone, which triggers the absorption of salt and water by the kidneys. Increasing the amount of fluid in the body also increases blood pressure. Proper blood pressure during fetal growth delivers oxygen to developing tissues, necessary for the normal development of the kidneys, especially for structures called the proximal tubules, and other tissues. In addition, angiotensin II may play a more direct role in kidney development, by influencing growth factors involved in the development of kidney structures.[10,11]

The genetic variation of the AGT gene that occurs in exon 2 involves a transition from thymine to cytosine which results in the replacement of methionine by threonine at amino acid position 235 to form the AGT gene variant M235T.[12-14] In this study, AGT gene mutations were found in 100% of the study subjects. AGT M235T CT gene variant was found in 37 subjects (51.38%), 19 subjects were male, 18 subjects were female. AGT M235T TT gene variant was found in 35 subjects (48.61%), 25 male subjects and 10 female subjects. This is contrary to the results of research from Mondry *et al*. (2005) which stated that the AGT M235T TT gene variant was found mostly in female subjects.[15]

The pathogenesis of essential hypertension is influenced by genetic and environmental factors. Mutations in genes related to hypertension can affect blood pressure through changes in salt and water reabsorption by nephrons. Genes of the renin-angiotensin system (RAS) have been studied extensively for their role in blood pressure control. Angiotensinogen (AGT) gene variants may be associated with an increased risk of essential hypertension. Case Control Study by Kooffreh *et al*. (2012) in a population involving 1308 subjects (612 hypertensive patients and 696 controls), ethnic Calabar and Uyo, Nigeria showed that the prevalence of homozygous AGT mutations was 88.4% in subjects with hypertension and 92.2% in subjects without hypertension, whereas for heterozygous mutations, the prevalence was 10.9% in subjects with hypertension and 7.5% in controls. In contrast to the results of Raharjo *et al*. (2013) who stated that the genetic variation of M235T angiotensinogen had no association with the incidence of essential hypertension in ethnic Southeast Sulawesi.[16] Study by Shamaa *et al*. (2015) who aimed to evaluate the frequency of the AGT (M235T) variant in relation to essential hypertension in a group of Egyptian residents found that there is a positive risk of developing essential hypertension if you have the T allele in both homozygous and heterozygous conditions. Out of a total of 24 subjects with hypertension in this study, 15 (62.5%) subjects had the AGT M235T CT gene variant, 9 other subjects had the AGT M235T TT gene variant.[17,18]

Subjects with wild type were not found in this study, this is because the prevalence of wild type is generally 0.3% in subjects with hypertension and 0.7% in subjects without hypertension (control). In this study the number of subjects was small, 72 people consisting of 24 subjects with hypertension and 48 subjects with normotension causing no wild type found.[19]

Angiotensinogen (AGT) is a central component of the renin-angiotensin system that controls systemic blood pressure and several other cardiovascular functions and may play an important role in the atherosclerotic pathway. In a study conducted by Al Najai et al in the Saudi population, the role of 8 AGT gene

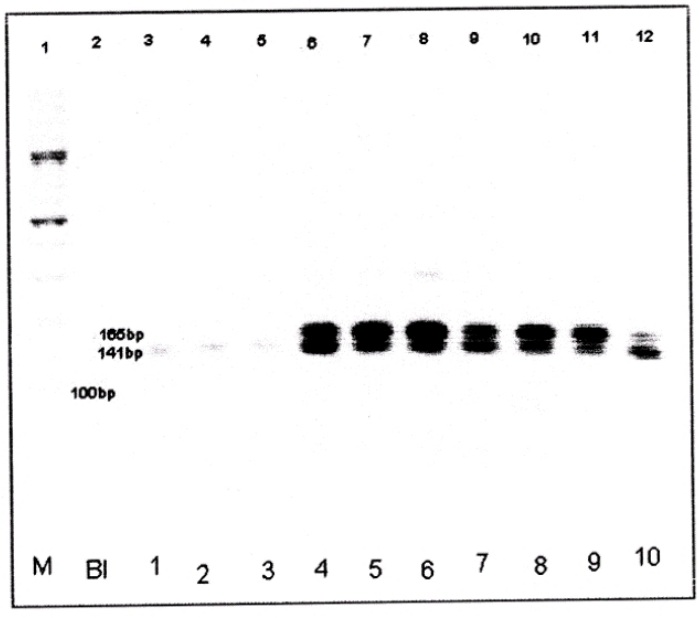

Figure 2. Analysis of gene variant AGT M235T

variants was evaluated in primary hypertension, type 2 diabetes mellitus (T2DM), and obesity. In this study, it was found that AGT is an independent risk gene for HTN, obesity and through the potential pleiotropic effect of AGT on the disease pathway leading to atherosclerosis.[18]

This study discusses the Angiotensinogen M235T gene in ischemic stroke patients in a population in Indonesia that has never been reported. A wider sample size and demographic variations of research subjects can be a development for this research topic.

CONCLUSION

Of the 72 samples analyzed, 3 variants of the Angiotensinogen M235T gene were found, namely CT, TT and CC variants. The AGT M235T CT gene variant was the most common variant, 37 (51.4%) samples.

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Original Article

The Effectiveness of Urinary Diversion in Patients with Cervical Cancer at Kariadi General Hospital

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Abstract

Background : Obstructive uropathy and hydronephrosis are common complications of cervical cancer. In order to provide an alternative route due to ureteral obstruction, urinary diversion was performed. Urinary diversion procedures are a therapeutic option for obstructive uropathy but their effectiveness is remain unclear. There is limited data that support urinary diversion as a treatment of ureteral obstruction to improve overall survival and progression-free survival. This study was aimed to determine the effectiveness of urinary diversion in the treatment of obstructive uropathy in cervical cancer patients.
Methods : This study is a cross sectional involved cervical cancer patients with symptoms of obstructive uropathy. Data were obtained from medical records and limited to patients admitted from May, 2020 to May, 2021. Primary outcome was urea level, creatinine level, stage of hydronephrosis and overall survival rate of patients.
Results : A total of 100 patients were included in the study. In both groups, the mean age of study subjects was 52–53 years with stage IIIB being the most widely reported. There was an improvement in post creatinine in the urinary diversion group. There was a significant difference in post creatinine levels between the non-urine diversion and urinary diversion groups (p=0.039). The 12-month survival rate, in the non-urinary diversion group had a value of 86% while the urinary diversion group had a value of 94%.
Conclusion : This study shows that urinary diversion procedure is effective in increasing the renal function and increasing the 12-month survival of cervical cancer patients with obstructive uropathy.

Keywords : Cervical cancer, Obstructive uropathy, Urinary diversion

INTRODUCTION

Cervical cancer is the second most common malignant tumor and one of the leading causes of cancer mortality in women. Persistent high-risk *human papillomavirus* (HPV) infection (serotypes 16 and 18) is considered as the main cause.[1] Over the past 30 years, the increase in the proportion of young women with cervical cancer has ranged from 10% to 40%.[2] In 2018 worldwide with an estimated 570,000 cases and 311,000 deaths, cervical cancer was the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women.[3]

Advanced cervical cancer patients often present with several life–threatening. Urinary tract obstruction due to cervical cancer mass accounts for about 11–44% of complications. Obstructive uropathy and hydronephrosis are common complications. Obstructive uropathy is usually a late manifestation of advanced disease, resulting from extrinsic compression of the ureter secondary to malignancy. The presence of ureteral obstruction and renal failure have a significant adverse effect on the survival of cervical cancer patients. In order to provide an alternative route due to ureteral obstruction, urinary diversion was performed.[4]

Urinary diversion is a surgical procedure to divert the normal flow of urine out of the body when the flow of urine is blocked. Percutaneous drainage of nephrostomy is associated with promising outcomes in terms of survival, improvement of renal function, pain, uremic symptoms and renal function status. Although urinary diversion procedures can certainly improve the outcomes of cervical cancer patients, current evidence suggests that urinary diversion does not significantly increase the survival rate of cervical cancer patients. This is related to previous studies, most of which were relatively long, involving relatively small cohort studies and many of them were retrospective.[4]

This study aims to determine the effectiveness of urinary diversion in the treatment of obstructive uropathy in cervical cancer patients.

METHODS

Study Design

This study is a cross sectional study. Data were obtained from medical records of cervical cancer patients undergoing urinary diversion for obstructive uropathy in Dr. Kariadi Central Hospital, Semarang. Data collection was limited to patients admitted from May, 2020 to May, 2021. This study has received ethical clearance from the local committee.

Study Populations

This study involved cervical cancer patients with symptoms of obstructive uropathy. Patients were stratified into two groups, those who required diversion and those who did not. The inclusion criteria were aged ≥18 years old, diagnosed with cervical cancer stage IIIb–IVa, had symptoms of obstructive uropathy, and underwent urinary diversion using ureteral stent or percutaneous nephrostomy. Exclusion criteria were diagnosed with kidney failure before the diagnosis of cervical cancer and there were other causes of obstructive uropathy besides cervical cancer.

Outcomes

Primary outcome was urea level, creatinine level, stage of hydronephrosis and overall survival rate of patients. Stage of hydronephrosis, urea and creatinine level were assessed early and after 12 months. This assesment is done to measure obstructive uropathy and patients renal function. Survival rates were assessed at 3, 6, 9, and 12 months after urinary diversion. Survival rates are estimated for each group and considered separately.

Statistical Analysis

Data analysis was performed using SPSS 26.0 series. Univariate analysis was conducted to determine the mean, standard deviation, median value, smallest value, largest value and frequency of patient baseline characteristic. Mann-Whitney U analysis was performed to determine differences in serum urea and creatinine values. The data is significant if $p<0.05$. Overall survival rate data analysis was conducted using the Kaplan Meier methods.

Ethical Clearance and *Informed Consent*

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institutional Research Committee at which the studies were conducted (approval number of the Health Research Ethics Committee of Dr. Kariadi General Hospital: No.1280/EC/KEPK-RSDK/2022). Informed consent was obtained from all individual participants included in this study.

RESULTS

Baseline Characteristics of Study Subjects

This study involved 100 patients who were divided into 2 groups, non-urinary diversion (n=50) and urinary diversion (n=50). There was a significant difference in cervical Ca stage between two groups (p=0.038). There was no significant difference in the stage of hydronephrosis at pre and post in the two groups. Urinary diversion does not improve the stage of hydronephrosis.

Comparison of Urea and Creatinine Levels

Creatinine levels were higher in non-urinary diversion group. There was a significant difference in post creatinine levels between the non-urinary diversion and

TABLE 1
Baseline characteristics of study subjects

Variable	Non-Urinary Diversion			Urinary Diversion			p
	n (%)	Mean ± SD	Median (min–max)	n (%)	Mean ± SD	Median (min–max)	
Age (years)	–	53.22±8.53	53 (35–73)	–	53.22±8.53	53 (35–73)	0.530[$]
Stage of Cervical Ca		–	–		–	–	**0.038**[#]
IIIB	48 (96)			39 (78)			
IVA	1 (2)			6 (12)			
IVB	1 (2)			5 (10)			
Systemic symptoms		–	–		–	–	–
Anemia	3 (6)			19 (38)			
Fatigue	11 (22)			24 (48)			
Nauseous	17 (34)			18 (36)			
Vomit	14 (28)			9 (18			
Anorexia	15 (30)			12 (24)			
Comorbidity		–	–		–	–	–
Hypertension	8 (16)			15 (30)			
Diabetes mellitus	4 (8)			12 (24)			
Urological symptoms		–	–		–	–	–
Dysuria	18 (36)			14 (28)			
Low back pain	10 (20)			14 (28)			
Intermittent	14 (28)			24 (48)			
Gynecological symptoms		–	–		–	–	–
Flux	27 (54)			31 (62)			
Fluor	26 (52)			22 (44)			
Hypogastric pain	9 (18)			10 (20)			
Stage of Hydronephrosis							
Pre		–	–		–	–	0.356[#]
No Hydroneprhosis	29 (58)			21 (42)			
Mild	11 (22)			12 (24)			
Moderate	7 (14)			13 (26)			
Severe	3 (6)			4 (8)			
Post		–	–		–	–	0.989[#]
No Hydroneprhosis	19 (38)			21 (42)			
Mild	17 (34)			15 (30)			
Moderate	10 (20)			10 (20)			
Severe	4 (8)			4 (8)			

[$]Independent T test; [&]Mann Whitney U; [#]Fischer Exact; [¥]Chi Square

TABLE 2
Comparison of urea and creatinine levels

Variable		Non-Urinary Diversion		Urinary Diversion		p
		Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
Urea	Pre	39.02±30.64	26.5 (11–155)	50.76±42.91	30 (9–156)	0.298[&]
	Post	44.74±22.31	40.5 (18–135)	64.06±58.20	41 (11–240)	0.637[&]
Creatinine	Pre	2.22±1.13	2 (0.8–5.8)	2.81±2.59	2.05 (0.1–12.7)	0.967[&]
	Post	2.53±0.91	2.4 (0.9–5.2)	2.38±1.69	1.7 (0.7–7.6)	**0.039[&]**

[&]Mann Whitney U

TABLE 3
The 12-month survival rate

Non-Urinary Diversion			Urinary Diversion		
Period	Status	Survival rate	Period	Status	Survival rate
3 month	Death	100%	3 month	Death	98%
6 month	Death	92%	6 month	Death	94%
9 month	Death	88%	9 month	Death	94%
12 month	Death	86%	12 month	Death	94%

urinary diversion group (p=0.039) (Table 2.). The urinary diversion is effective in increasing renal function of cervical cancer patients with obstructive uropathy.

Survival Rate

Within 12 months, in non-urinary diversion group there were 7 subjects died, where 1 subject died at month 4, 2 subjects died at month 5, 1 subject died at month 6, 2 subjects died at month 9 and 1 subject died in month 11. In the urinary diversion group, there were 3 subjects died, where 1 subject died at month 3 and 2 subjects died at month 4.

The 12-month survival rate, in the non-urinary diversion group had a value of 86% while the urinary diversion group had a value of 94%. The urinary diversion is effective in increasing 12-month survival rate of cervical cancer patients with obstructive uropathy.

DISCUSSION

Baseline Characteristics of Study Subjects

In both groups, the mean age of study subjects was 52–53 years with stage IIIB being the most widely reported. Pratiwi SE, e*t al.* in their study on the profile of cervical cancer patients at Soedarso Hospital obtained similar results that the highest incidence of cervical cancer occurred in the age range of 41–60 years, where most of the patients came with stage IIIB (45.4%).[5] In Indonesia, almost 1.8/1000 population (all ages) suffer from cancer with the peak prevalence at the age of 45–65 years. Meanwhile, in West Kalimantan, 1.5/1000 people suffer from cancer. In the European population, the incidence of cervical cancer begins to increase at the age of 20–29 years and progressively increases until around the age of 45–49 years. In the United States, the chances of developing invasive cervical cancer are also higher in women aged 40 to 59 years.[6] In India, the peak age for cervical cancer is 40 to 49 years.[7] In Indonesia, a study conducted in Surabaya from March to August 2016 stated that cancer patients were dominated by ages 41–60, mode was 51 years, and the average was 48 years.[8]

Histological characteristics are significant independent prognostic factors in cervical cancer. Squamous cell carcinoma (SCC) is the most common histologic feature of cervical cancer, accounting for three-quarters of all cases. Age at first sexual intercourse, smoking, suppression of the immune system, use of oral contraceptives, high parity (multiple pregnancies), and human papillomavirus (HPV) infection have all been associated with the development of cervical cancer.[9]

The most systemic symptoms in the non-urinary diversion group were nausea and anorexia, whereas in the urinary diversion group were weakness and anemia. The most frequently reported comorbid by both groups

was hypertension.

Nausea, and vomiting are frequently reported side effects in patients receiving chemotherapy. This side effect has the potential to lead to a patient's refusal to continue the chemotherapy. The incidence and severity of nausea, vomiting and vomiting in patients receiving chemotherapy varies, depending on the type and dose of chemotherapy, drug combination, and individual characteristics. These unpleasant sensations can appear, either as a result of treatment or the disease itself and significantly affect the patient's quality of life and adherence to therapy.[10]

Nausea and vomiting are usually more severe in the next cycle, especially in the fourth cycle and a significant predictor in the fifth cycle.[11] One study found that in combination therapy (radiation and chemotherapy), patients reported more symptoms of distress than chemotherapy alone.[12] Patients receiving combination therapy with radiation and chemotherapy experienced a significantly higher rate of symptom occurrence than those receiving chemotherapy alone. This suggests that combination therapy is an important factor contributing to the experience of nausea-vomiting symptoms. The stage of the cancer may also be another factor that contributes to the symptoms of nausea and vomiting. The potential causes of nausea and vomiting in cancer patients are numerous, especially in those with advanced or metastatic disease.[10] When cervical cancer progresses to a more advanced stage, symptoms begin to appear. The advanced stage of the disease is a predictor of acute nausea and vomiting. One study found that symptom experience was significantly higher in patients with advanced stages (Stage III and IV) than patients in the early stage group. Previous study involved stage II and III cervical cancer patients without comorbidities. Therefore, the stage of the disease is thought to contribute to the rate of nausea and vomiting.[12]

Anemia is common in cervical cancer patients. Iron deficiency and tumor bleeding are common causes of anemia in cervical cancer. Anemia has a negative prognostic effect, and correction is thought to improve the prognosis. Therefore, most patients will receive transfusion and/or erythropoietin treatment.[13] Obstructive uropathy increases intrarenal pressure which causes suppression of kidney function. The closer intrapelvic pressure approaches the glomerual filtration pressure (6–12 mmHG), the less urine can be secreted. Glomerular filtration rate and renal plasma flow are reduced, concentrating power is gradually lost, anda the urea creatinine concentration ratio of urine is lower than normal kidney. This condition will lead to stages of uremia. Anemia may be found secondary to advanced bilateral hydronephrosis(stage of uremia).[14]

Cancer patients usually have several comorbidities.[15] There is evidence that a higher burden of comorbidites is associated with poorer survival for cancer patients.[16] The prevalence of comorbidities varies between population groups and may contribute to the distribution of cancer survival. These findings are consistent with previous study from New Zealand.[17] Hypertension is very common among adults and is associated with significant morbidity and mortality, including heart attack, stroke, chronic kidney disease and death. Therefore, hypertension remains the most important risk factor for many cardiovascular disorders. Vascular resistance increases with age because vascular walls become less elastic. These changes combined with common age-related conditions such as heart failure that reduce cardiac output result in an increased incidence of hypertension in the elderly.[18]

The most frequently reported urological symptom in the non-urinary diversion group was dysuria, whereas in the urinary diversion group it was intermittent. The most frequently reported gynecological symptoms in both groups were flux and fluor.

The clinical presentation of obstructive uropathy is highly variable and often depends on the site of the obstruction.[19] In pelvic malignancies, both acute and chronic presentations of obstructive uropathy may occur, with etiologies ranging from stricture due to pelvic surgery,[20] radiation-induced scar tissue formation within the ureter or extrinsically in the retroperitoneum, external ureteral compression from either the primary tumor, recurrent masses, or metastases.[19]

Obstruction at the level of the bladder neck, also known as bladder outlet obstruction (BOO), can be caused by a benign process or a malignant process such as invasion of the bladder in or distal to the triangle. Patients often complain of obstructive and irritating voiding symptoms, such as urgency, frequency, decreased power of the stream, and incomplete emptying of the bladder.[21]

Pre-cancerous changes to the cervix usually do not cause pain or other symptoms and are not detected unless a woman undergoes an examination. Symptoms generally do not appear until abnormal cervical cells become cancerous and invade nearby tissues. The most common symptoms are foul-smelling vaginal discharge, abnormal bleeding or inter-menstrual bleeding, postcoital bleeding, postmenopausal bleeding or back pain.[22]

The most frequently reported stage of pre-hydronephrosis in the non-urinary diversion group was mild, whereas in the urinary diversion group it was moderate. Urea and creatinine pre-levels were higher in the urinary diversion group, with a mean of 50.76 mg/dL and 2.81 mg/dL, respectively. The most frequently reported stage of post hydronephrosis in the two groups was mild. Post-ureum levels were higher in the urinary diversion group (64.06 mg/dL) while higher post-creatinine levels were found in the non-urinary diversion group (2.53 mg/dL).

Hydronephrosis occurs when an obstruction in the

collecting system of the kidney causes distention of the renal calyces. Women with cervical cancer often develop this complication as a result of a tumor or lymph node disorder, inflammation, or scarring of the pelvic rim. In addition, cervical cancer is often treated with nephrotoxic drugs, which are sometimes dosed or omitted when hydronephrosis occurs in association with renal insufficiency. Such dose changes can compromise cancer treatment and potentially lead to decreased clinical outcomes. Patel K, *et al.* in their study of hydronephrosis in cervical cancer patients stated that the development of hydronephrosis was directly related to advanced cancer stage ($p<0.0001$), squamous histology ($p=0.0079$), and non-surgical treatment modality ($p=0.0039$). Of the 278 patients based on survival data, 221 lived with a median follow-up of 1.5 years (range 0.025.4 years).[23]

The presence of ureteral obstruction and hydronephrosis is a sign of advanced disease because it indicates parametrial involvement. This condition may be accompanied by electrolyte and blood urea nitrogen (BUN) disturbances and high serum creatinine levels. Uremia often complicates the case and can lead to a decrease a level of consciousness and even death if left untreated. Previous studies have shown that as the malignancy progresses, patients may develop stage 4 chronic kidney disease and require further treatment. A study investigating the survival of patients treated with radiotherapy found that women with stage T3b cervical cancer (17 patients) and hydronephrosis had a lower 5-year survival rate compared to those without hydronephrosis (26% vs. 41%).[24] Goklu *et al.* found that the median survival of patients with unilateral hydronephrosis was significantly greater than that of patients with bilateral hydronephrosis (42.2 vs 29.9 months).[25] Patel *et al*. reported that the most prominent symptom of hydronephrosis was urinary tract infection (9 of 17 patients), accompanied by pain (8 of 17 patients). In their series of studies, they observed that 7 patients had renal failure with creatinine levels ranging between 1.7 and 5.6 mg/dL.[26]

Dienstmann *et al*. investigated the impact of the procedure on 50 patients with recurrent cervical cancer and observed that 60% experienced improvement in renal function and a decrease in mean of creatinine level of 2.7 mg/dL (from 6.4 pre-procedure to 3.7 mg/dL post-procedure). Twenty-nine patients (58%) died of renal failure and median survival was 8.9 weeks.[27]

Patients presenting with hydronephrosis due to pelvic sidewall disease have previously been shown to have a poor clinical outcome. Urinary diversion procedures can be used to avoid blockages and improve kidney function. Successful use of urinary diversion improves quality of life and survival.[28]

Survival Rate

At 12 months, more subjects died in the non-urinary diversion group than in the urinary diversion group. The results of this study are similar to those of Beckta JM *et al.* who assessed urinary diversion as a local management of advanced cervical cancer and found that 79% of non-diverted patients were alive while 60% of patients were alive at the end of 22 months of follow-up. As a result of tumor size Primary or large pelvic lymphadenopathy, 14% to 34.5% of women present with ureteral obstruction at the time of initial diagnosis. This obstruction can lead to hydronephrosis and impaired renal function, which may preclude aggressive treatment with Cisplatin-based chemotherapy. However, renal function may be improved if the ureteral obstruction is removed by insertion of a ureteral stent or percutaneous nephrostomy. Ureteral stent placement is considered first-line therapy for obstructive uropathy, although it is technically difficult to measure the size of a malignant mass. In contrast, in the context of external ureteral compression, percutaneous nephrostomy is a simpler procedure but carries an increased risk of infection and decreased quality of life.[29]

This study result that the 12-month survival rate, in the non-urinary diversion group had a value of 86% while the urinary diversion group had a value of 94%. Choudhury S, *et al*.[30] who assessed the role of urinary diversion in patients with advanced cervical cancer with obstructive uropathy stated that the improvement in kidney function was evidenced by a decrease in serum creatinine levels from an average of 4.98 mg/dl to 2.33 mg/dl. Improved quality of life was seen in 68% of cases. Thus, palliative urinary diversion is effective in patients with obstructive uropathy with complications of advanced cervical malignancy because it results in a significant improvement of renal function as well as quality of life.

CONCLUSION

This study shows that urinary diversion procedure is effective in increasing renal function and 12-month survival of cervical cancer patients with obstructive uropathy.

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Original Article

The Correlation of Nutritional Status and Phase Angle in Hemodialysis Patient

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Abstract

Background : Nutritional problem are often experienced by patients with chronic kidney disease (CKD) undergoing regular hemodialysis. There are various tools that can be used to evaluate nutritional status, such as the 7-point Subjective Global Assessment (SGA), nevertheless, malnutrition in these patients is still underdiagnosed and resulting in worse clinical outcomes. Phase Angle (PhA) as measured by multi-frequency Bioelectrical Impedance Analysis (BIA) may detect nutritional problem in early stage in order to start nutrition therapy early. The objectives of this study was to analyze correlation between nutritional status and PhA in CKD patients with regular hemodialysis.
Methods : The subject of this study were 39 CKD patients undergoing regular hemodialysis who met the inclusion and exclusion criteria. Nutritional status was evaluated by 7-point SGA, while PhA was measured by multi-frequency BIA. Correlation between variables analyzed by Spearman correlation test.
Results : Positive correlation was observed between nutritional status and PhA ($r = 0.64$; $p < 0.001$). There was a negative correlation between PhA and number of comorbids ($r = -0.381$, $p = 0.017$). PhA was not correlated with sex and hemodialysis duration.
Conclusion : There is positive correlation between nutritional status measured by 7-point SGA and PhA in CKD patients with regular hemodialysis.

Keywords : CKD, Hemodialysis, Nutritional Status, 7-point SGA, Phase Angle

INTRODUCTION

Patients with end-stage chronic kidney disease (CKD) need renal replacement therapy, either kidney transplant or regular dialysis, such as hemodialysis. Hemodialysis patient has a greater risk of nutritional disorder. However, nutritional disorders are often detected too late or even completely neglected in daily clinical practice. This will not only cause a lot of harm from a medical perspective such as poorer prognosis, complications, and quality of life, but also the economic aspect.[1] Various tools to evaluate nutritional status are available. One particular tool that is recommended for CKD patients is 7-point Subjective Global Assessment (SGA), which is a modified SGA and has been recommended by the National Kidney Foundation Kidney Disease/Dialysis Outcomes and Quality Initiative (NKF K/DOQI) to be used as a nutritional evaluation tool in CKD patient.[2] 7-point SGA is widely used because it has been validated and is commonly used in patients in nephrology departments.[1,2] However, various nutritional status evaluation tools including 7-point SGA require skilled examiners. Subjectivity between examiners often occurs which causes the difference in results.[3,4]

Phase Angle (PhA) is one particular measurement from multi-frequency bioimpedance analysis (BIA) which is obtained from the calculation between the reactants and the electric current resistance produced by the multi-frequency BIA, which is described in degrees. PhA can identify nutritional disorders at an early stage, thus nutritional disorders could be detected as early as possible. Early diagnosis allows nutritional intervention to be given at an earlier stage, consequently improve nutritional status, clinical conditions, and patient outcomes.[5,6] PhA value is considered normal range between 6° to 7°, even reaching 8.5° or more in athletes, while the PhA value below 5° associated with malnutrition.[7] In contrast to other nutritional status evaluation tools, the PhA examination does not depend on anthropometric results. It is a distinct advantage in patients who are difficult to measure an accurate anthropometric examination such as CKD patients who generally have a fluid overload.[8]

Previous studies reported that PhA had a close correlation with nutritional status in various groups of patients. However, studies related to the correlation between nutritional status and PhA in hemodialysis patients has not been widely studied in Indonesia. The researcher wanted to analyze the correlation between nutritional status as measured by the 7-point SGA and PhA in CKD patients undergoing hemodialysis at the hemodialysis unit of RSUP Dr. Kariadi.

METHODS

This study is a correlational study with secondary data. Subjects were CKD patients undergoing regular hemodialysis at the Hemodialysis Unit of RSUP Dr. Kariadi and have met the inclusion and exclusion criteria. The sample size was calculated using formula :

$$n = \left\{ \frac{(Z\alpha + Z\beta)}{0{,}5 \ln \{(1+r)/(1-r)\}} \right\}^2 + 3$$

with α = 5%, β = 20%, and r value based on previous research is 0.561. Based on these calculations, minimum sample size is 23 subjects.

The independent variable is nutritional status, while the dependent variable is PhA. The confounding variables that influenced the study and were to be measured were sex, number of comorbidities, and duration of hemodialysis. The inclusion criteria for this study were CKD patients undergoing hemodialysis at the Hemodialysis Unit of RSUP Dr. Kariadi in the study period, aged ≥18 years to <60 years, had BMI ≤30 kg/m^2, and complete medical record data. The exclusion criteria for this study were patients with anasarca edema, severe ascites, and patients who were pregnant.

Data with a nominal or ordinal scale are shown in terms of number (%), while data with a ratio or interval scale are shown in terms of mean ± standard deviation and median value [range of values]. Data normality test using Shapiro-Wilk. Data on nutritional status as measured by the 7-point SGA were not in normal distribution and hence analyzed with Spearman's correlation. The correlation of PhA with sex was analyzed using the chi-square test, while the correlation of PhA with the number of comorbidities and duration of hemodialysis was analyzed using the Spearman test. This research has received permission from the Health Research Ethics Committee of RSUP Dr. Kariadi with No. 1159/EC/KEPK-RSDK/2022. Data confidentiality is maintained according to the provisions of ethical clearance. Research-related costs are fully funded by the researcher.

RESULTS

There were 39 subjects who participated in this study, the majority of subjects were male (66.7%). The mean age was 49.4 ± 8.55 years. The youngest and oldest age ranges were 30 years and 59 years respectively. BMI cut-off in this study was <30 kg/m^2. The mean BMI in the subjects was 23.2 ± 3.42 kg/m^2 with a median value of 23.1 kg/m^2. More than half of the subjects were overweight, moreover, only 3 people or 7.7% were in the underweight group. Comorbid diseases recorded in this study were hypertension, diabetes mellitus, and cardiovascular disease. Nearly 85% of subjects had at least 1 comorbid, with hypertension being the most common. The mean duration of hemodialysis was 26.6 ± 27.1 months with the

TABLE 1
Subject Characteristics

Subject Characteristics	Mean ± SD	Median [value range]	(%)
Age (year)	49.4±8.55	52 [30–59]	–
Sex			
Male	–	–	26 (66.7)
Female	–	–	13 (33.3)
BMI (kg/m^2)	23.2±3.42	23.19 [18.22–29.11]	
Underweight	–	–	3 (7.7)
Normoweight	–	–	14 (35.9)
Overweight	–	–	10 (25.6)
Obese	–	–	12 (30.8)
Number of comorbidities			
Unknown	–	–	6 (15.4)
1 comorbidity	–	–	20 (51.3)
2 comorbidities	–	–	11 (28.2)
3 comorbidities	–	–	2 (5.1)
Type of comorbidities			
Hypertension	–	–	26 (66.7)
Diabetes mellitus	–	–	17 (43.6)
Cardiovascular disease	–	–	5 (12.8)
Duration of hemodialysis (month)	26.6±27.1	13 [1–96]	–
Nutritional status	3.9±1.03	4 [2–6]	–
Normal	–	–	3 (7.7)
Moderate malnutrition	–	–	33 (84.6)
Severe malnutrition	–	–	3 (7.7)
Phase angle	4.7±0.91	4.9 [2.9–6.3]	–

shortest being 1 month and the longest being 96 months. The mean value of nutritional status as measured by the 7-point SGA in this study was 3.9 ± 1.03 with a median value of 4. More than 90% of the subjects were malnutrition, and only 7.7% were in the category of normal nutritional status. PhA is the dependent variable in this study. The average PhA was 4.7 ± 0.91 with a mean value of 4.9. The lowest PhA value in this study was 2.9, while the highest PhA value was 6.3. The characteristics of the subjects are described in Table 1.

The correlational hypothesis test between nutritional status, measured by the 7-point SGA, and PhA using the Spearman test are shown in Table 2. The results obtained an r = 0.641 and p = <0.001. The p value <0.05 indicates a statistically significant correlation, with a conclusion that between nutritional status and PhA, there is a moderate positive correlation.

This study included 3 confounding variables to be analyzed, namely sex, number of comorbidities, and duration of hemodialysis. The correlation test between PhA as the dependent variable and sex is shown in Table 3, the correlation test between PhA and the number of comorbidities is shown in Table 4, and the correlation test between PhA and the duration of hemodialysis is shown in Table 5.

PhA analysis with sex using the chi-square test. PhA value <5° is associated with malnutrition, hence used as a limit for PhA value. However, this PhA values

TABLE 2
Correlation of Nutritional Status with Phase Angle

Variable	r	p
Nutritional status	0.641	<0.001
Phase angle		

TABLE 3
Correlation of Phase Angle with Sex

Sex	Phase Angle	
	< 5°	≥ 5°
Male	13 (50%)	13 (50%)
Female	7 (53.6%)	6 (46.2%)

X^2=0.000; df=1; p=1.000

TABLE 4
Correlation of Phase Angle with Number of Comorbidities

Number of comorbidities	Phase Angle (°)	r	p
0	5.53±0.82	-0,381	0.017
1	4.79±0.81		
2	4.30±0.96		
3	4.80±0.71		

TABLE 5
Correlation of Phase Angle with Duration of Hemodialysis

Variable	r	p
Duration of hemodialysis	0.030	0.858
Phase angle		

limit was obtained from studies with subjects who were dominated by Caucasian. There are no studies yet on PhA values for the Mongoloid like this study. Based on this test, p value >0.05 was obtained which indicated that there was no significant difference between the PhA values based on sex.

The Spearman correlational test between PhA and the number of comorbidities showed r = -0.381 and p = 0.017. The value of r = -0.381 indicates the opposite correlation between the two, and the value of p<0.05 indicates that there is a significant correlation between the number of comorbidities and PhA.

The Spearman correlation test between the duration of hemodialysis and PhA showed a value of r = 0.030 and a value of p = 0.858. The p value > 0.05 showed no significant correlation between PhA and the duration of hemodialysis.

DISCUSSION

The test results showed no significant difference between the PhA values and sex. The majority of the subjects were male. This data is similar to study in India and Israel in 2011 and 2014 respectively with the results of 69.6% and

63.2% of subjects were male.[9,10] More recent study in Medan, Indonesia and China also showed the results were not much different, with respectively 71.2% and 54.9% of the subjects being male.[11,12]

The subjects mean age is 49.4 ± 8.55 years. Studies on CKD patients with regular hemodialysis in India and Medan, Indonesia showed similar results with 49.5 years and 46.3 years for the male and female patient groups in India, while the mean age 46.1 years in Medan, Indonesia.[10,11] Studies in China and Israel showed higher mean age, 58.02 years and 68.7 years, respectively.[9,12] This difference could be due to age-related criteria, patients who are in the elderly group according to Indonesian law (have reached the age >60 years) are not included in this study.[13,14]

The mean BMI in this study is 23.2 ± 3.42 kg/m^2 with a median of 23.1 kg/m^2. The mean BMI in studies with CKD patients with regular hemodialysis in China and Medan, Indonesia showed similar results, 21.33 kg/m^2 and 21.45 kg/m^2, respectively. Slightly different results were obtained from Israel, with the subject's average BMI being 26.6 kg/m^2.[9,11,12] This difference is due to racial differences in each country which has a different BMI categorization as well. According to WHO, the normal BMI rate in Israel is between 18.5–24.9 kg/m^2, while in Indonesia and other Asia Pacific countries are 18.5–23.9 kg/m^2.[15]

This study used 7-point SGA to determine the nutritional status of CKD with regular hemodialysis. The results showed that 92.3% of the subjects were malnourished, although most of them were in moderate malnutrition. A study on CKD patients with regular hemodialysis in India and Medan, Indonesia also used SGA and its modifications to determine nutritional status. In a study in India, 96.9% of subjects were malnourished, while in a study in Medan, Indonesia, 65.4% of subjects were malnourished, and the majority of subjects were moderately malnourished.[10,11]

Statistical analysis in this study showed a positive moderate correlation. This is consistent with various previous studies, such as studies in China and Medan, Indonesia, which stated that there was a significant correlation between nutritional status and PhA. The nutritional disorder experienced in this study was disease-related malnutrition (DRM). DRM is associated with a decrease in body cell mass (BCM) and a shift of intracellular water (ICW) to extracellular water (ECW), resulting in a change in the ECW/ICW ratio. Thus, a decrease in BCM and a change in the ECW/ICW ratio causes lower PhA values.[11,12,16]

Several confounding variables may affect the PhA value. The confounding variables examined in this study were sex, number of comorbidities, and duration of hemodialysis. Study on healthy subjects in Brazil showed male has a better PhA value than female. This cannot be separated from the differences in free-fat mass (FFM) scores and ECW ratios which were higher in the male than in the female.[17] The statistical analysis between sex and PhA in this study was not significant. This might happen because subjects had at least one of the three comorbid diseases, namely hypertension, diabetes mellitus, and/or cardiovascular disease, and 92.3% of subjects were malnourished. CKD patients with regular hemodialysis are at high risk of malnutrition, even though malnutrition causes changes in body composition in the form of decreased muscle mass, fat mass, to impaired fluid status.[1] CKD patients with regular hemodialysis had significantly lower FFM and ECW ratios than healthy individuals.[12] In this study, subjects were CKD patients and the majority were malnourished, rather than in good health, which led to a non-significant correlation between sex and PhA in this study.

Data analysis in this study showed a negative correlation between the number of comorbidities and PhA, hence the higher the number of comorbidities, the lower the PhA value. This is similar to the previous study, that comorbidity will significantly worsen PhA values. Comorbidities are associated with inflammation, malnutrition, and worse functional capacity which will worsen PhA values.[16,18] Hypertension was the most common comorbid in this study followed by diabetes mellitus, with 66.7% of subjects having hypertension and 43.6% of subjects having diabetes. mellitus. Study in India showed similar characteristics regarding the type of comorbidity, with 72.7% of subjects having hypertension and 45.5% of subjects having diabetes mellitus.[10]

Duration of hemodialysis is one of the factors that affect the PhA value. The mean duration of hemodialysis in this study was 26.6±27.1 months. Similar characteristics were found in India with a mean duration of hemodialysis being 25.3 months and 24.9 months for male and female respectively, and another study in Medan, Indonesia showed a mean of 24.2 months. The study in Medan, Indonesia did not analyze the correlation between the duration of hemodialysis and nutritional status, while in this study and the study in India, the duration of hemodialysis did not show a significant correlation.[10,11] Contrast results were reported in Korea. A study in Korea reported the mean duration of peritoneal dialysis was 57.5 months, and had a significant correlation between the PhA value and the duration of peritoneal dialysis. This is following the previous explanation that hemodialysis aims to save lives and improve the quality of life for patients diagnosed with CKD, however, in the long term might contribute to several complications related to nutritional status such as muscle wasting and malnutrition.[19,20] The different results of PhA value and duration of hemodialysis in this study compared to study in Korea could be due to the tendency to delay the initiation of hemodialysis in the subjects of this study. A study conducted at RSUPN Dr. Cipto Mangunkusumo, Jakarta shows that there is a

tendency of up to 90% to delay referring ESRD patients who require initiation of hemodialysis. The poor mobilization ability and low adherence are the main factors for the delay.[21] RSUP Dr. Kariadi, similar to RSUPN Dr. Cipto Mangunkusumo, is a national referral center hospital, thus delays in the initiation of hemodialysis may also occur in the subjects of this study. The delay in referral made the hemodialysis initiation data in this study not reflect the actual condition of disease progression. Patients who require but do not undergo hemodialysis are associated with poor clinical outcomes such as increased morbidity and mortality.[22]

There are several limitations to this study. The wide age range is one of the limitations of this study. This study uses the criteria of adult age between ≥ 18 years to <60 years. Comorbid in this study were limited considering this study used secondary data. This causes some unknown comorbidities that might affect the analysis. Another limitation of this study is the initiation of hemodialysis was not investigated further. The delay in the initiation of hemodialysis can affect the analysis in this study, especially related to the duration of hemodialysis. The delay in the initiation of hemodialysis causes the recorded duration of hemodialysis to not accurately reflect the progress of the disease, which can lead to bias.

CONCLUSION

This study showed a positive correlation between the independent variables, nutritional status examined by the 7-point SGA, with PhA as the dependent variable. Results analysis showed no significant correlation between PhA with the duration of hemodialysis and sex. The only confounding variable in this study that showed a significant correlation with PhA was the number of co-morbidities in subjects.

The results indicate the high prevalence of nutritional disorders in CKD patients undergoing hemodialysis and the importance of PhA in identifying nutritional disorders. PhA examination can provide its clinical advantages, considering the difficulty of accurate anthropometric examinations in CKD patients, which are often undetected by other tools. A decrease in the PhA value could provide an early warning of nutritional disorder, hence, nutritional counseling and intervention could be given as early as possible.

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Original Article

Effect of Adding Kinesiotaping on Chronic Phase Post Stroke Rehabilitation Receiving Weight Shifting Training on Walking Speed

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Abstract

Background : Stroke is the leading cause of disability including decreased walking speed. It is estimated that 73% of stroke sufferers have a lack of motor control and result in limited mobilization. Kinesiotaping(KT) is a method that can be added to other forms of exercise including weight shifting training. With the addition of kinesiotaping is expected to occur improvements in muscle performance and balance so that the speed of walking increases. The objectives of this study was to prove the effect of the addition of KT on chronic stroke rehabilitation that gets weight shifting training on walking speed.
Methods : This study is a randomized controlled trial pre-test and post test control group design. There were 18 subjects of chronic stroke rehabilitation patients divided into 2 groups, namely the control group that got weight shifting training (9 people) and the treatment group that got the addition of kinesiotaping to weight shifting training (9 people). The walking speed assessment was measured before and after 4 weeks of treatment.
Results : There was a significant difference in the mean walking speed before and after treatment in each group ($p<0.001$). In the treatment group 0.60 ± 0.08 and 0.68 ± 0.07 at the end. In the control group 0.62 ± 0.05 at the beginning and 0.64 ± 0.05 at the end. There was a sigificant difference in the mean walking speed increase in both groups ($p<0.001$).
Conclusion : The mean increased walking speed was higher in the group that got the addition of KT in chronic phase stroke rehabilitation who received weight shifting training.

Keywords : stroke, walking speed, weight shifting training, kinesiotaping

INTRODUCTION

Stroke is one of the neurological syndromes that can cause disability in human life. Data in Indonesia shows a trend of increasing stroke cases both in terms of death, incidence, and disability.[1] Stroke patients are generally disturbed by asymmetrical postures, reduced voluntary control of movement and balance that does not normally affect walking ability which can increase the risk of falling. Research shows that 84% of stroke patients have motor involvement of more than one joint, and 76% have ankle joint involvement. Muscle weakness and ankle joint instability cause drop foot in stroke patients which is the main factor for gait disturbance in stroke patients. This disorders will cause a decrease in walking speed which can interfere daily activities.[2,3]

There are many techniques to improve walking speed. Various neurofacilitator techniques can be used to facilitate weak muscle contractions in stroke survivors. Recently, kinesiotaping (KT) can be used for musculoskeletal conditions to improve muscle function. Improved balance and muscle control through KT can increase walking speed.[4] The ability to initiate and control weight shifts is a requirement for independent walking. Study from Jung *et al.*, 2014 reported that weight shift training is beneficial in improving trunk control and proprioception in stroke patients with chronic hemiparesis.[5] This study assessed the effect of adding KT in post-acute stroke patients who received weight shifting training on increasing walking speed.

METHODS

The study design was a randomized controlled trial in patients with chronic phase stroke rehabilitation who were members of the stroke community at Dr Kariadi Hospital and Elisabeth Hospital Semarang. The study was conducted with the approval of the Ethics Commission of the Faculty of Medicine, Diponegoro University Semarang Number 280/EC/KEPK/FK-UNDIP/XII/2020. The study was conducted on January 18 - March 2, 2021. The method of taking subjects was consecutive sampling and simple randomization.

. Inclusion criteria included post-stroke patients with first attack > 6 months and < 5 years, age 50–60 years, able to maintain standing position ≥ 5 minutes and able to walk independently without aids 50 meters (without looking at gait), normal vision or if any visual impairment has been corrected, no cognitive impairment, ankle spasticity MAS score 1–2, ankle dorsiflexor muscle strength at least 3. Exclusion criteria include uncontrolled hypertension (blood pressure >180/110), patients with hemispatial neglect, vestibular, proprioception, and perception disorders, there are open wounds or non-specific skin diseases in the kinesiotaping application area, hypersensitivity to kinesiotaping materials, diabetes mellitus with GDS levels >250 mg/dl or accompanied by sensory disturbances. The drop out criteria were if the patient did not do weight shifting training and kinesiotaping was not applied for more than 2 days within the time span of the study.

Total subjects were 18 people, divided into 9 subjects in each group. Randomization was carried out using a simple method, in which the subject took an envelope containing one of the groups. In the treatment group, participants received a home program in the form of weight shifting training and KT application, while in the control group, participants only received weight shifting training. The treatment was carried out for 4 weeks. KT application is carried out for 5 days interspersed with 1 day rest before the next KT application. Assessment of walking speed was carried out before and at the end of the 4th week of the study.

KT application was carried out on the tibialis anterior muscle by facilitation and on the gastrocnemius muscle by inhibition. The principle of weight shifting training involves lower limbs that experience weakness by giving or transferring the patient's body weight without moving the leg position.

The results of the normality test for data distribution using the Shapiro Wilk test showed that the data were normally distributed in age, stroke duration, VO2max, walking speed, and height. Data that is not normally distributed, namely BMI. The normally distributed data were tested using the unpaired t-test while those that were not normally distributed were tested by the Mann Whitney U test. The hypothesis test for differences before and after treatment used a paired t-test because the data was normally distributed. All data is processed with the help of a computer using SPSS® software. Significance in this study was obtained if a p value <0.05 was obtained with a 95% confidence interval.

RESULTS

The characteristics of the study subjects in both groups at the initial examination of all the variables mentioned in Table 1, there was no significant difference between the treatment group and the control group with a p value >0.05.

The effect of adding kinesiotaping to weight shifting training on the walking speed of post-stroke rehabilitation patients in the chronic phase can be seen in Table 2.

The initial walking speed before treatment in the treatment group was 0.60±0.08 meters/second and in the control group 0.62±0.05 meters/second with a value of p=0.523. For the final walking speed after treatment in the treatment group 0.68±0.07 meters/second and the control group 0.64±0.05 meters/second with a value of p = 0.185.

In Table 2, it can be seen that there is a significant difference in the average walking speed before and after

TABLE 1
Characteristics of subjects

Characteristics		Group		p
		Treatment (n=9)	Control (n=9)	
Age (years)		55.78±3.03	55,78±2,64	1.000§
Gender	Male	7 (77.8%)	7 (77.8%)	1.000¥
	Female	2 (22.2%)	2 (22.2%)	
Stroke Duration (months)		21.00±7.28	21.00±7.28	1.000§
Hemiparese	Dextra	7 (77.8%)	7 (77.8%)	1.000¥
	Sinistra	2 (22.2%)	2 (22.2%)	
BMI (kg/m^2)		21.85±1.18	21.74±0.98	0.825‡
BH (centimeter)		161.00±2.83	161.56±3.91	0.734§
Activity	Low	7 (77.8%)	7 (77.8%)	1.000¥
	Moderate	2 (22.2%)	2 (22.2%)	
MMT ankle dorsiflexor	3	1 (11.1%)	1 (11.1%)	1.000¥
	4	8 (88.9%)	8 (88.9%)	
VO2 max		10.48±0.89	10.35±0.70	0.730§
BBS		43.11±1.27	44.00±1.87	0.255§

Information: §Independent t; ¥Chi square; ‡Mann whitney
BMI : Body Mass Index; BH : Body Height; MMT : Manual Muscle Test; BBS : Berg Balance Scale

TABLE 2
Comparison of the Walking Speed of the Treatment and Control Groups

Walking Speed	Group		p
	Treatment (n=9)	Control (n=9)	
Early	0.60±0.08	0.62±0.05	0.523§
End	0.68±0.07	0.64±0.05	0.185§
p	<0.001¶*	<0.001¶*	
Delta	0.08±0.02	0.02±0.01	<0.001§*

Information: *Significant (p < 0.05); § Independent t; ¶ Paired t

treatment in each group (p <0.001). The mean increase (delta) of walking speed in the treatment group was 0.08 ± 0.02 meters/second and in the control group 0.02±0.01 meters/second. From the statistical test showed that there was a significant difference in the average increase in walking speed in the two groups (p <0.001).

DISCUSSION

Disruption of gait patterns in stroke patients during the stance phase and swing phase will result in a decrease in cadence (number of steps per minute), stride length (activity that occurs between the time the heel of the foot touches the floor with the heel of the same foot touching the floor again), step length (activities that occurs between the heel of one foot with the heel of the other foot) and there is an increase in step width.[6,7]

In this study, the group that was only given weight shifting training experienced a significant increase in walking speed before and after treatment (0.02 ± 0.01 meters/second; p<0.001). This is in accordance with the results of a study by Anderson *et al.* in 2015 which

reported an improvement in gait and ambulation in chronic phase stroke patients.[8]

In stroke patients, the patient tends to shift the body's weight towards the healthy side of the leg so that learned disuse occurs. Weight shifting training exercises can overcome this so that there is an increase in balance through postural control and proprioceptive improvement and can improve gait patterns during the stance phase. Someone with a bad balance tends to have a longer stance phase than normal people. With weight shifting training, the stance phase becomes more balanced between the healthy side and the parese side so that there is an increase in stride length and cadence which will increase walking speed.[5,9]

In the treatment group that received additional KT, there was a significant difference in the increase in walking speed before and after treatment (0.08 ± 0.02 meters/second; $p<0.001$). Significant differences were seen in the mean increase in walking speed between the control and treatment groups ($p<0.001$). This shows that the addition of KT in the medical rehabilitation phase of chronic stroke that receives weight shifting training can significantly increase walking speed. In Jung *et al.*'s study it was reported that there was an increase in the value of balance function which was thought to be directly related to an increase in sensorimotor function in the form of improved coordination, muscle strength and flexibility in the lower limbs. With this improvement, walking patterns will improve and result in an increase in walking speed.[5]

Installation of KT with facilitation techniques on the tibialis anterior muscle makes the insertion and origin close to the center of mass, as well as the muscle fibers, fascia and skin above it. This KT stretch will facilitate muscle movement through peripheral feedback regulation to the central nervous system resulting in an increase in muscle contraction and relaxation of the antagonist muscles. In addition, the tibialis anterior muscle which is facilitated by KT also improves the ankle strategy. The ankle joint not only supports the body through weight bearing and leg muscle function, but also provides sensory information and continuously stimulates a sense of posture control through the foot's contact with the ground during movement. The function of the tibialis anterior muscle is to stabilize the ankle when the foot hits the ground during the stance phase and then acts to lift the foot off the ground during the swing phase. Thus, activation of the tibialis anterior muscle is also important for ankle stability and proprioception.[10,11]

In chronic phase stroke patients, muscle weakness contributes greatly to gait disturbances. One of them is the weakness of the dorsiflexor muscles which will cause impaired walking mobility function which is characterized by a decrease in walking speed, where the patient shows a walking pattern with circumduction to make leg clearance which is difficult to do.[4] Application of KT with facilitation techniques on the tibialis anterior muscle which is a primary ankle dorsiflexor can maintain the ankle in a dorsiflexed position and can prevent or reduce the occurrence of drop foot when walking thereby helping the patient in ground clearance. By allowing for foot clearance, there is a significant increase in walking speed.[11]

In stroke patients there is parese on one side, so the patient tends to rely on the healthy side which results in difficulties in doing weight shifting training. Therefore, the addition of KT in post-stroke chronic phase patients who receive weight shifting training will help improve the ankle joint strategy, facilitate the contraction of the tibialis anterior muscle who experience weakness and reduce gastrocnemius muscle tone. Thus the addition of this KT will facilitate the exercise to be more optimal.[4,10]

In accordance with the results of a study by Sheng Y, *et al*. in 2019 on sixty chronic phase stroke patients with foot drop which stated that immediately after facilitating KT application to the tibialis anterior muscle, there was an increase in the walking balance ability of stroke patients with drop foot. In this study, we used KT in facilitation for the tibialis anterior muscle and inhibition for the gastrocnemius muscle.[11]

Application of KT with inhibition techniques on the gastrocnemius muscle makes the insertion and origin away from the center of mass, as well as the muscle fibers, fascia, and overlying skin so that KT stimulation will inhibit muscle contraction through peripheral feedback regulation to the central nervous system and will reduce muscle contraction and increase antagonist muscle contraction. This resulted in reduced spasticity of the gastrocnemius muscles resulting in better ankle dorsiflexion. Inhibition techniques in the gastrocnemius muscles help reduce spasticity that occurs in chronic phase stroke rehabilitation patients. By decreasing muscle tone through stimulation of an inhibitory kinesiotaping stretch on the gastronemius muscles, the muscles work better.[4,11]

In muscles and tendons, KT can improve its function through mechanical receptors, namely the Golgi tendon organ in the muscle tendon junction. The Golgi tendon organ controls the muscle spindles during movement. Stimulation of mechanoreceptors with the application of KT inhibition of the gastrocnemius muscle through the Achilles tendon will inhibit the Golgi tendon organ thereby helping to regulate the tone of the gastrocnemius muscle. Thus the spasticity of the gastrocnemius muscles is reduced.[10,12]

CONCLUSION

The results of this study indicate that the addition of KT in the post-stroke chronic phase rehabilitation that receives weight shifting training will increase the average walking

speed higher. The addition of KT can be used in the chronic phase of post-stroke rehabilitation to increase walking speed. In the next study, follow-up could be carried out 1 month after treatment to determine the duration of effectiveness of adding KT in the chronic phase of post-stroke rehabilitation that received weight shifting training.

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Original Article

In-Hospital Major Adverse Cardiovascular Events in Patients with STEMI during COVID-19 Pandemic

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Abstract

Background : The Coronavirus Disease 2019 (COVID-19) pandemic has become a global burden, changing healthcare system and affecting patients with ST segment elevation myocardial infarction (STEMI). Several countries reported a decrease in hospital admission, changing management, increase total ischemic time, and major cardiovascular events (MACE) in the pandemic era. However, there is limited data especially in Indonesia. The objectives of this study was to know the differences in admissions, characteristics, management and in-hospital MACE in STEMI patients between pre and pandemic era.

Methods : Comparative observational analytical study was done on 169 patients in the pre-pandemic (12 March 2019–11 March 2020) compared to 163 patients in the pandemic era (12 March 2020–30 September 2021) with STEMI at Dr. Kariadi Semarang Hospital. Assessment of monthly admission rates, total ischaemic time, reperfusion management, COVID-19 status and MACE were carried out.

Results : During the COVID-19 pandemic, there was a decrease in the average admission of 14.1 to 8.6 patients per month (p<0.001), increase total ischaemic time of 8.78 (3.22-19.68) hours to 10.22 (3 .20–20.43) hours (p<0.001), decreased use of primary PCI (97.0% vs. 83.4%, p<0.001), increased fibrinolytic (1.8% vs8.6%, p=0.010) and no reperfusion (1.2%vs8.0%, p=0.007). There was a significant increase in MACE in the era of the COVID-19 pandemic (10.7%vs22.1%, p=0.008), with mortality (4.7%vs11.7%, p=0.035), stroke (1.2%vs1.8%, p=0.680), cardiogenic shock (4.1%vs11.0%, p=0.030), and acute pulmonary edema (3.6%vs10.4%, p=0.024).

Conclusion : There was a decrease in admissions and primary PCI procedure, increase use of fibrinolytics and without reperfusion, total ischemic time prolongation, and significant increase of in-hospital MACE in STEMI patients during the COVID-19 pandemic.

Keywords : ST-segment elevation myocardial infarction, COVID-19 pandemic, total ischaemic time, management, major adverse cardiac event

INTRODUCTION

Since the Coronavirus Disease 2019 (COVID-19) pandemic which began in Wuhan, China, in December 2019, there has been a sharp increase in confirmed patients, which has led to changes in health services and community restrictions. The phenomenon of the COVID-19 pandemic does not only affect patients with COVID-19 but has a wider impact. In fact, to date, there have been several studies reporting a reduction in hospital admission rates in STEMI patients.[1–7] In China, it was stated that there was a 51.4% decrease in STEMI patient admissions and an increase in patients who did not get reperfusion compared to 2018 and 2019.[1] There is a study in five hospitals in Indonesia that reports a significant reduction in STEMI patients from 338 to 190 patients in 2020, as well as a decrease in the use of primary PCI.[7] In addition to a decrease in admissions, there has also been an increase in delays, both delays for patients coming to health facilities (patient delay) and prolonged time in the health care system (hospital delay). Several studies found that the time from the onset of typical ischemia symptoms to first medical contact (FMC) and ischemic time increased significantly.[1,7–11] Meta-analysis study by Zhu *et al*. that compared the characteristics and outcomes of STEMI patients found that in six articles there were an increase in onset to FMC time (SMD 0.51, 95% CI, 0.24-0.78, p<0.001) in the COVID-19 pandemic era compared to before the COVID-19 pandemic.[12]

In addition, there were several studies that reported an increase in poor outcomes in STEMI patients during the pandemic era. The China Chest Pain Center's conducted a study on 28,189 STEMI patients from 2019-2020. Apart from finding a decrease in admissions to health services and a change in reperfusion strategy, there was also an increase in the incidence of death in hospital (OR 1.21; 95% CI: 1.07-1, 37;p=0.003) and heart failure (OR 1.10;95% CI: 1.02-1.18; p=0.020).[13]

The differences in health services between developed and developing countries, such as hospital availability, early screening and rapid microbiological examination, availability of an isolation catheterization rooms, and geographical differences allow for differences in outcomes in this population. As a result, it is necessary at this time to investigate and analyze differences in admissions, characteristics, management, and in-hospital MACE in STEMI patients between the pandemic era and before the pandemic era.

METHODS

This was an observational study with a cross-sectional design. Total sampling was carried out on STEMI patients at Dr Kariadi General Hospital Semarang in the period March 12 2019 to March 11 2020 in the group before the COVID-19 pandemic era and March 12 2020 to September 30 2021 for the COVID-19 pandemic era group with STEMI diagnosis criteria based on symptoms (eg persistent chest pain) and signs (eg 12-lead ECG) consistent with myocardial ischemia.[14] The inclusion criteria for this study were patients aged 18 to 80 years, and diagnosed with STEMI onset (typical infarction of chest pain in the emergency room of Dr. Kariadi General Hospital, Semarang) ≤ 12 hours. Exclusion criteria were having an eGFR value <30 ml/min/1.73m^2, known to have cancer which is thought to be the main cause of death during treatment and having incomplete medical record data. Identity and demographic data were collected, as were clinical data in the form of complaints, onset, last COVID-19 status during treatment, cardiovascular risk factors, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, Killip class, infarction location based on ECG criteria, hemoglobin level, random blood glucose level, creatinine level, drugs administered, data related to fibrinolytic reperfusion, Primary PCI, onset to FMC time, FMC to needle time, FMC to wire crossing time, cath lab activation time, total ischaemic time, number of vessel disease, final TIMI flow, and MACE during treatment, death cause, stroke, urgent revascularization, acute pulmonary edema, and acute heart failure.

Data will be displayed in the form of mean ± standard deviation, median (min–max), frequency and percentage. An unpaired comparative test was carried out, Chi-Square test was used in categorical variables, unpaired t-test on numeric variable (parametric) or Mann Whitney (non-parametric). The normality of data distribution was tested by the Kolmogrov–Smirnov test. The p value <0.05 is a significant value. Statistical analysis used the IBM SPSS version 23.0. This study was conducted after obtaining permission from Health Research Ethics Commission No.1083/EC/KEPK-RSDK/2022 and research permission by Dr. Kariadi General Hospital No DP.02.01/I.II/3159/2022.

RESULTS

There are 332 samples of STEMI patients were obtained in the period of March 12 2019 – September 31 2021. The number of samples on the period before the COVID-19 pandemic era on March 12 2019 – March 11 2020 were 169 samples and the period during the COVID-19 pandemic era on March 12 2020 – September 31, 2021 were 163 samples (Table 1) and displayed in a graph per month (Figure 1). The baseline characteristics of the patients are shown in Table 1. There was a significant decrease in STEMI patient admissions per month, with an average of 14.1±3.1 before the pandemic compared to 8.6±4.1 during the COVID-19 pandemic. There was also a significant decrease in the use of primary PCI from 164 (97.0%) to 136 (83.4%), p 0.001, as well as a significant increase in the use of fibrinolytics from 3 (1.8%) to 14 (8.6%), p=0.010, and

TABLE 1
Baseline Characteristics

Variables		All research samples (n=332)	Before COVID-19 Pandemic (n=169)	COVID-19 Pandemic (n=163)	p
Admissions, patients per week		2,5	3.1	1.9	
Age, years		57.6±9.1	57.9±8.3	57.1±9.9	0.414§
Sex	Male	279 (84.0%)	135 (79.9%)	144 (88.3%)	0.051¥
	Female	53 (16.0%)	34 (20.1%)	19 (11.7%)	
Cardiovascular Risk Factor	Hypertension	193 (58.1%)	99 (58.6%)	94 (57.7%)	0.955¥
	Diabetes	160 (48.2%)	77 (45.6%)	83 (50.9%)	0.386¥
	Dyslipidemia	105 (31.6%)	52 (30.8%)	53 (32.5%)	0.823¥
	Active smoker	145 (43.7%)	72 (42.6%)	73 (44.8%)	0.143¥
	Ex-smoker	82 (24.7%)	36 (21.3%)	46 (28.2%)	
	Family History	30 (9.0%)	12 (7.1%)	18 (11.0%)	0.289¥
	Menopause	44 (14.2%)	28 (87.5%)	16 (88.9%)	0.631£
Presentation Method	Referred from other hospital	246 (74.1%)	114 (67.5%)	132 (81.0%)	**0.007¥**
	Self presenting	86 (25.9%)	55 (32.5%)	31 (19.0%)	
Systolic BP, mmHg		119 (67–180)	113 (71–175)	124 (67–180)	**0.002‡**
Heart Rate, bpm		79 (31–126)	80 (46–126)	78 (31–120)	**0.024‡**
Killip class	1	270 (81.3%)	139 (82.2%)	131 (80.4%)	
	2	42 (12.7%)	23 (13.6%)	19 (11.7%)	
	3	7 (2.1%)	3 (1.8%)	4 (2.5%)	
	4	13 (3.9%)	4 (2.4%)	9 (5.5%)	
	1		139 (82.2%)	131 (80.4%)	0.765¥
	2+3+4		30 (17.8%)	33 (19.6%)	
Anterior Infarction		168 (50.6%)	85 (50.3%)	83 (50.9%)	0.997¥
BMI, kg/m^2		24,7 (±2.9)	24,6 (±2.8)	24.8 (±3.1)	0.479§
Creatinine, mg/dL		1,1 (0.5–2.6)	1.1 (0.5–2.6)	1.2 (0.5–2.6)	**0.037‡**
Blood Glucose, mg/dL		142 (65–558)	145 (71–530)	130 (65–558)	0.419‡
Reperfusion Method	Primary PCI	300 (90.4%)	164 (97.0%)	136 (83.4%)	**<0.001¥**
	Fibrinolysis	17 (5.1%)	3 (1.8%)	14 (8.6%)	**0.010¥**
	None	15 (4.5%)	2 (1.2%)	13 (8.0%)	**0.007¥**
	Reperfusion	317 (95.5%)	167 (98.8%)	150 (92.0%)	**0.007¥**
	No reperfusion	15 (4.5%)	2 (0.6%)	13 (3.9%)	
Treatment	Aspirin	332 (100%)	169 (100%)	163 (100%)	
	P2Y12i	332 (100%)	169 (100%)	163 (100%)	0.568¥
	Ticagrelor	250 (75.3%)	130 (76.9%)	120 (73.6%)	

TABLE 1. Continued

Variables		All research samples (n=332)	Before COVID-19 Pandemic (n=169)	COVID-19 Pandemic (n=163)	p
	Clopidogrel	82 (24.7%)	39 (23.1%)	43 (26.4%)	
	Anticoagulant	213 (64.2%)	107 (63.3%)	106 (65.0%)	0.832¥
	Heparin	31 (9.3%)	7 (4.1%)	24 (14.7%)	
	Fondaparinux	165 (49.7%)	91 (53.8%)	74 (45.4%)	
	Enoxaparin	17 (5.1%)	9 (5.3%)	8 (4.9%)	
	ACEi/ARB	306 (92.2%)	155 (91.7%)	151 (92.6%)	0.914¥
	Beta blocker	263 (79.2%)	127 (75.1%)	136 (83.4%)	0.084¥
	Statin	332 (100%)	169 (100%)	163 (100%)	
COVID-19		2 (0.6%)	0 (0%)	2 (1.2%)	0.240£

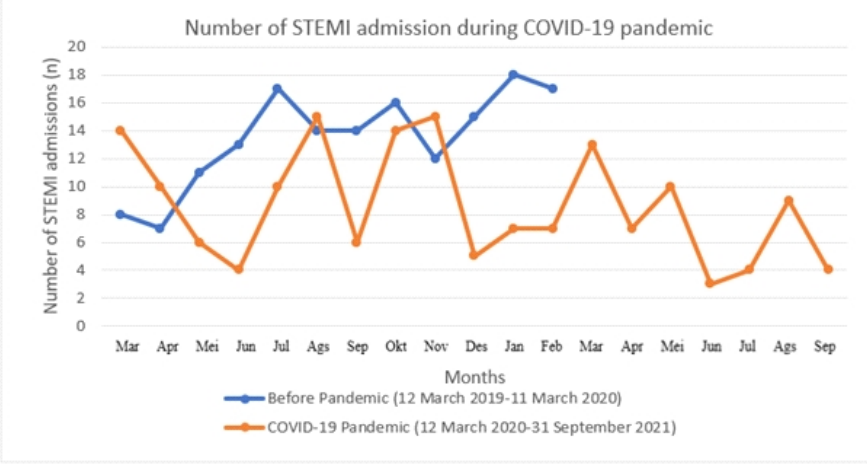

Figure 1. Monthly admission comparison of STEMI patients in one year before pandemic (12 March 2019 – 11 March 2020) and during the COVID-19 pandemic (12 March 2020– 31 September 2021)

without reperfusion from 2 (1.2%) to 13 (8.0%), p=0.007 (Table 1, Figure 2). The majority of patients were men, with an average age of 57.9±8.3 before the pandemic and 57.1±9.9 during the pandemic. There were no significant differences in cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, smoking, and family history. The number of patients who came to the hospital with referrals from other health facilities increased sharply from 114 (67.5%) to 132 (81.0%) p=0.007. There were 2 (0.6%) patients with a confirmed diagnosis of COVID-19 during treatment. Procedural data of patients who underwent reperfusion are included in Table 2 with details, namely that a significant prolongation of the total ischemic time component was obtained in the pre-pandemic era with 8.78 (3.22–19.68) hours compared to 10.22 (3.20–20.43) hours (Table 2, Figure 3) which includes an onset component of 5.0 (1.5–12.0) hours compared to 7.0 (1.0–12.0) hours, door to wire crossing of 3.28 (1.17–12.68) hours versus 3.66 (0.55–9.85) hours, and door to needle (on fibrinolytics) 0.58(0.30–0.66) hours versus 1.70 (0.91–2.20) hours. Patients receive the same medical treatment before and during the COVID-19 pandemic. Major cardiovascular events significantly increased in the pandemic era with a total of 36 (22.1%) compared to 18 (10.7%) patients in the pre-pandemic era p=0.008 (Table 3, Figure 4).

DISCUSSION

During the COVID-19 pandemic period, there was a significant decrease in the average patient admission per month from the pre-pandemic era versus the pandemic era from 14.1±3.1 patients per month compared to 8.6±4.1 patients per month, p <0.001, mean diff 5.50, CI 95%

TABLE 2
Procedural data of patients undergoing reperfusion

Variables		Research samples (n=317)	Before COVID-19 Pandemic (n=167)	COVID-19 Pandemic (n=150)	p
Onset, hours		6.4 (1.0–12.0)	5.0 (1.5–12.0)	7.0 (1.0–12.0)	**<0.001‡**
Door-to-wire crossing, hours		3,37 (0.55–12.68)	3.28 (1.17–12.68)	3.66 (0.55–9.85)	**0.046‡**
Total ishcemic time (Primary PCI), hours		10.01 (3,22–20,43)	8.96 (3.22–19.68)	10.53 (3.95–20.43)	**<0.001‡**
Door-to-needle, hours		1.46 (0.30–2.20)	0.58 (0.30–0.66)	1.70 (0.91–2.20)	**0.008‡**
Total ishcemic time (Fibrinolitik), hours		6.70 (3.20–12.00)	5.66 (4.30–7.58)	7.00(3.20–12.00)	0.705‡
Total ishcemic time (Primary PCI +fibrinolitik), hours		9.55 (3.2–20.43)	8.78 (3.22–19.68)	10.22 (3.20–20.43)	**<0.001‡**
CAD vessel disease	1	92 (29.8%)	38 (23.2%)	54 (37.2%)	
	2	92 (29.8%)	56 (34.1%)	36 (24.8%)	
	3	125 (37.7%)	70 (42.7%)	55 (37.9%)	
	1+2	184 (59.5%)	94 (42.7%)	90 (62.1%)	0.463¥
	3	125 (40.5%)	70 (57.3%)	55 (37.9%)	
Infarct Related Artery	LAD	158 (47.6%)	84 (51.2%)	74 (51.0%)	
	LCx	15 (4.5%)	7 (4.3%)	8 (5.5%)	
	RCA	133 (40.1%)	72 (43.9%)	61 (42.1%)	
	LAD+RCA	1 (0.3%)	1 (0.6%)	0 (0%)	
	LM	2 (0.6%)	0 (0%)	2 (1.4%)	
Final TIMI flow	3	286 (86.1%)	150 (91.5%)	136 (93.8%)	
	2	22 (6.6%)	13 (7.9%)	9 (6.2%)	
	1	1 (0.3%)	1 (0.6%)	0 (0%)	
	3	286 (86.1%)	150 (91.5%)	136 (93.8%)	0.574¥
	1+2	23 (7.4%)	14 (8.5%)	9 (6.2%)	

2.88–8.13 (Figure 1). This significant decrease in patient admissions also occurred globally, in London, England with a significantly decreased incidence of STEMI per week (15±3.5 in 2019 vs 10±4.4 in 2020, p=0.013).[15] Another study in Indonesia at five hospitals with primary PCI facilities stated a decrease in STEMI patient admissions in February – June 2020 (190 patients) compared to the same period in 2019 (338 patients).[7] The decline in STEMI patients during the COVID-19 pandemic may be due to several factors, including the patient's fear of going to health services at the hospital, especially with primary PCI services, where the hospital is larger and has full capacity to avoid transmission of COVID-19.[7,13,15] Some patients who want to check themselves out choose health services in places that tend not to be crowded.[7,13,15] Other factors, namely the lockdown policy, orders to stay at home, and social distancing, are also causes of a decrease in STEMI admissions to hospitals.[15,16] These policies can reduce stress factors, improve healthy lifestyles such as diet, sports activities, and good sleep quality, which can prevent acute myocardial infarction.[15–18] Reduction in air pollution was also reported during the policy, which could reduce exposure for individuals which is also thought to reduce the occurrence of acute myocardial infarction.[15] Focus on public education about COVID-19 and reduced education regarding awareness, signs, and symptoms of life-threatening diseases such as STEMI can cause people to perceive chest pain or shortness of breath as a respiratory symptom. This has the potential to reduce the number of patients requiring emergency care.[15,16]

This study's significant increase in patient presentation with the referral method is also similar to the registry of The International Study on Acute Coronary

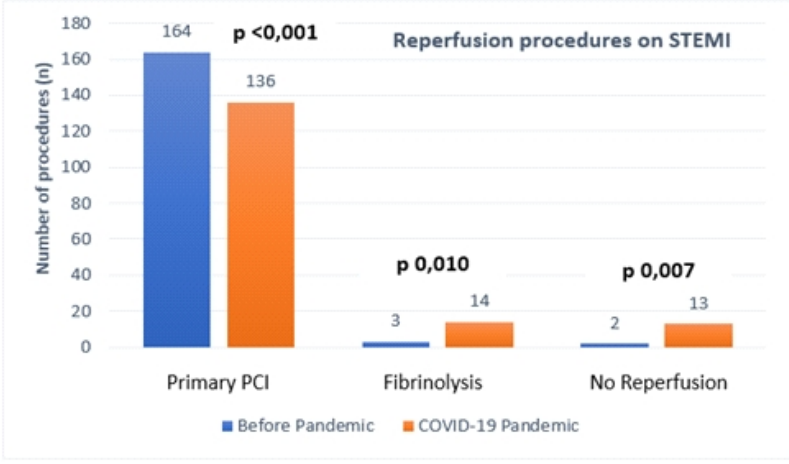

Figure 2. Comparison of STEMI patient reperfusion methods before and during the COVID-19 pandemic.

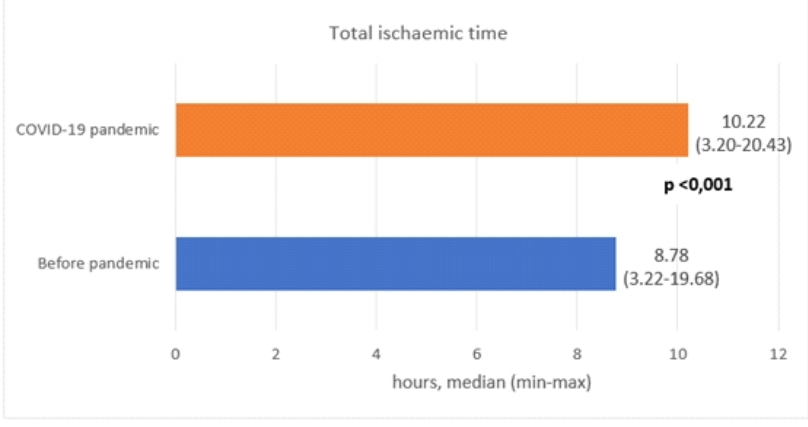

Figure 3. Comparison of total ischemic time in STEMI patients before and during the COVID-19 pandemic.

TABLE 3
In-hospital outcomes

Variables	All Research samples (n=332)	Before COVID-19 Pandemic (n=169)	COVID-19 Pandemic (n=163)	p
MACE	54 (16.3%)	18 (10.7%)	36 (22.1%)	**0.008**[¥]
Death	27 (8.1%)	8 (4.7%)	19 (11.7%)	**0.035**[¥]
Stroke	5 (1.5%)	2 (1.2%)	3 (1.8%)	0.680[£]
Urgent Revascularization	0	0	0	
Cardiogenic shock	25 (7.5%)	7 (4.1%)	18 (11.0%)	**0.030**[¥]
Acute Lung Edema	23 (6.9%)	6 (3.6%)	17 (10.4%)	**0.024**[¥]

Note : The values displayed are mean ± SD, median (min–max), or n (%).
[‡]Mann Whitney; [§]Independent t; [¥]Chi Square, [£]Fischer. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; BMI, body mass index; MACE, major adverse cardiac event; BP, blood pressure; TIMI, thrombolysis in myocardial infarction

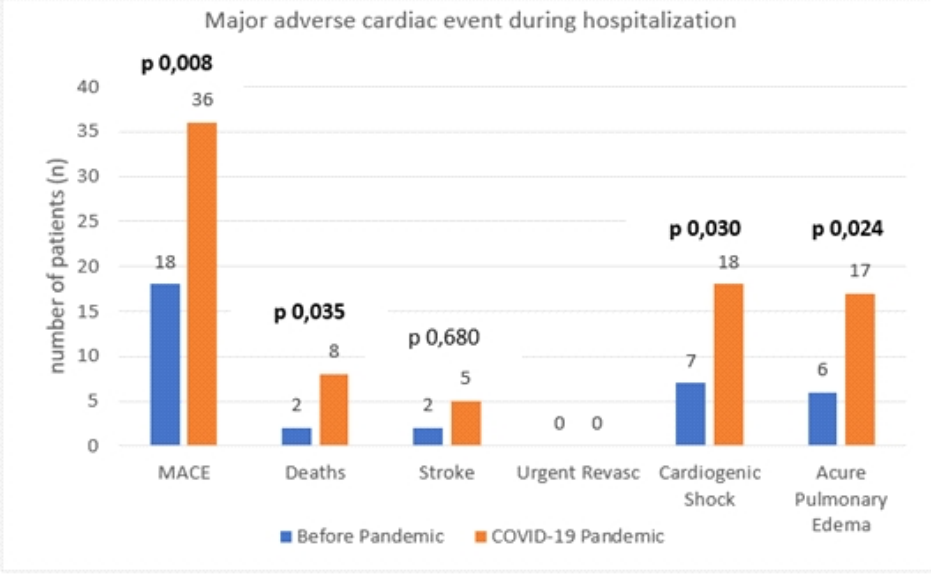

Figure 4. Comparison of the MACE components in STEMI patients before and during COVID-19 pandemic.

Syndromes- ST Elevation Myocardial Infarction COVID-19 (ISACS-STEMI COVID-19) in 6,609 patients who underwent Primary PCI in 18 countries, which stated an increase in referral rates to hospitals with Primary PCI using ambulances (from the community) from 1,893 (54.3%) patients in 2019 to 1,639 (58.3%) patients.[19,20] The increase in the number of referrals to hospitals with primary PCI facilities during this pandemic era was due to the patients' fear of avoiding transmission of COVID-19 where hospitals with primary PCI facilities are usually large hospitals, which also receive referrals for COVID-19 patients.[2,7,20] The full capacity of hospitals, especially with primary PCI facilities, also resulted in patients tending to seek health services that weren't crowded, so that the percentage of referred patients to hospitals with primary PCI increased.[2,7,20]

There was a significant decrease in the use of primary PCI in the pandemic era by 136 (83.4%) patients compared to before the COVID-19 pandemic by 164 (97.0%) patients with p<0.001; IK95% 2,210–14,185; a significant increase in the use of fibrinolytics by 14 (8.6%) patients compared to 3 (1.8%) patients with p=0.010; IK95% 1,417-16,524 (Figure 2). The ISACS-STEMI COVID-19 registry in 109 hospitals reported a consistent reduction in the use of primary PCI in STEMI patients, with an average of 559 (95% CI 514 – 607) in 2019 compared to 477 (95% CI 435 – 522) per million population in 2020.[19,20] Whereas in Indonesia, there was also an increase in the percentage of conservative management of STEMI patients in June 2020 (33.3%) compared to the same month in 2019 (11.7%).[7] At this time, we found a shift in reperfusion strategy in STEMI as an adaptation to COVID-19 which has a high transmission rate. The Chinese protocol recommends thrombolysis with COVID-19 in isolation wards for all acute STEMI patients (onset within 12 hours and without thrombolysis contraindications).[13] This is similar to the 1st edition of the COVID-19 management protocol in April 2020 which was also prepared by Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI).[21]

However, along with the dynamic status of the COVID-19 pandemic, the latest COVID-19 management guidebook published in January 2022 (ed 4) has the principle that timely reperfusion must be pursued during the COVID-19 pandemic.[22,23] In this guideline, PERKI is guided by ESC, where reperfusion must still be carried out in STEMI patients while paying attention to the safety of health workers. In the absence of previous COVID-19 testing, all STEMI patients must be managed as if they were positive for COVID-19. This guideline also states that all primary PCI procedures are carried out in facilities capable of performing PCI in patients with confirmed COVID-19 (isolation catheterization room).[22,23] Due to the lack of isolation catheterization room facilities at Dr. Kariadi Semarang Hospital and the duration of COVID-19 screening, which requires antigen and PCR tests, all patients with STEMI onset within 12 hours and a positive COVID-19 initial screening did not receive a primary PCI strategy.

In this study, fibrinolytics were performed on 14 patients, with details on 12 patients having successful fibrinolytics, where 8 patients were continued with early routine PCI, and 2 patients with failed fibrinolytics were continued with rescue PCI. Of all the patients who underwent fibrinolytic therapy, three MACE were obtained with details of 2 patients dying and 1 patient

experiencing acute pulmonary edema. This is different from the pre-pandemic era, where only 3 fibrinolytic therapies were performed and success, with no one had MACE. Furthermore, in our study, we found 13 patients without reperfusion therapy, where two patients had confirmed COVID-19, one patient had suspected COVID-19 and three patients barely made it past the onset of 12 hours. With details of 2 patients with positive COVID-19 confirmation, the first patient with inferior STEMI KILLIP 1 underwent conservative therapy, and the second patient with anterior STEMI accompanied by ARDS pneumonia underwent conservative therapy. So that the increase in the use of fibrinolytics and without reperfusion that occurred in this pandemic era has been proven to increase the incidence of MACE.

A significant increase in duration of patient onset from first feeling infarction symptoms to first medical contact was also found in the pre-COVID-19 era, with a median mean time of 5.0 (1.5-12.0) hours compared to 7.0 (1.0–12.0) hours in the era of the COVID-19 pandemic (p<0.001). A meta-analysis that compared the characteristics and outcomes of STEMI patients said that six articles found an increase in the onset to FMC time (SMD 0.51, 95% CI, 0.24–0.78, p<0.001) during the pandemic era compared to before the COVID-19 pandemic.[12] One of the reasons for this lengthening of time is due to the patient's fear of seeking health facilities due to COVID-19 which was obtained from interviews during hospital admission.[9,12] The full capacity of hospitals during several periods during the COVID-19 pandemic in Indonesia also made it more difficult for patients to seek medical assistance, so that the onset would be even longer.

In this study, the total duration of ischemic time in patients receiving reperfusion was found to be prolonged during the COVID-19 pandemic era with a median length of 10.22 (3.20–20.43) hours compared to 8.78 (3.22–19.68) hours in the pre-pandemic era p<0.001 (Figure 3). There was also increased median total ischemic time with fibrinolytic from 7.00 (3.20–12.00) hours compared to 5.66 (4.30–7.58) hours with p=0.705; the median door to needle time also experienced a significant increase with 1.70 (0.91–2.20) compared to 0.58 (0.30–0.66) hours with p=0.008. The ISACS-STEMI COVID-19 registry states that the total ischemic time was prolonged >12 hours for 196 (120–355) minutes in 2019 compared to 225 (135–410) in 2020 (p<0.001) and door to balloon time for 40 (25–64) minutes in 2019 compared to 40 (25–70) minutes in 2020 (p=0.01).[19] The lengthening of the total ischemic time, especially the system delay component, is seen in the significant lengthening of door to cathlab activation and door to crossing wire. Where the lengthening of time in the STEMI service system occurs due to a screening examination protocol before the patient enters the emergency unit and preparations for the use of personal protective equipment (PPE) for health workers, including doctors, so as to delay the diagnosis and initial management of STEMI, after that the patient is still subject to a rapid test , complete blood count, chest x-ray examination, and CT scan.[7,12,24] Preparation of personnel and equipment in the isolation catheterization room is also called increasing the length of the total ischemic time.[20]

Patient delay in our study was the component that made the main contribution to the lengthening of the total ischemic time during the COVID-19 pandemic with a median difference of 5.0 (1.5–12.0) hours compared to 7.0 (1.0–12.0) hours in the era of the COVID-19 pandemic (p <0.001). As a result, health service counseling provided by health workers and the government has been critical in combating fear of COVID-19 infection, particularly in emergency situations, where STEMI patients at this time are expected to benefit from prompt and appropriate medical attention because this population has a high risk of MACE.[7]

In the era of the COVID-19 pandemic from March 12 2020 to September 31 2021 with a total of 163 patients, 2 (1.2%) had a confirmed diagnosis of COVID-19. In addition, the researchers conducted a further search on all patients and found 11 patients with STEMI who were confirmed positive for COVID-19. However, 9 patients could not be included in this study sample due to late onset (>12 hours), incomplete ischemic time data, and evidence of myocarditis. There is still a possibility that some patients will be confirmed because in the early days of the COVID-19 pandemic they only used rapid screening which included clinical data on signs and symptoms, chest x-ray, blood laboratory, and contact history and demographics. The limited and long duration of testing for COVID-19 using RT-PCR at the start of the COVID-19 pandemic also led to a reduction in the number of STEMI patients undergoing standard tests to diagnose COVID-19.

The MACE rate increased significantly during the pandemic era, rising from 36 (22.1%) to 18 (10.7%) patients prior to the COVID-19 pandemic, with p=0.008. Mortality, cardiogenic shock, and acute pulmonary edema also increased significantly, with a ratio of 19 (11.7%) vs 8 (4.7%) p=0.035, 18 (11.0%) vs 7 (4.1%) p=0.030, and 17 (10.4%) vs. 6 (3.6%) p=0.024. Meanwhile, the incidence of stroke did not increase significantly in the pandemic era, namely 3 (1.8%) compared to 2 (1.2%) with p=0.680 and there were no patients requiring urgent revascularization in both groups (Figure 4). The ISACS-STEMI COVID-19 registry also reported the same thing, namely the death rate increased significantly in 2020 compared to 2019 (481 deaths (6.5%) vs 457 deaths (5.3%); OR 1.26, CI 95% ,1.10–1.4, p<0.001).[19] As a comparison above shows, MACE rates reported in European countries were lower during the pandemic and before the pandemic, where more optimal STEMI management was able to reduce mortality and MACE compared to this

study. In addition, the differences in the assessed MACE outcomes and the different study populations are also other reasons. While the increase in MACE rates during this pandemic was mentioned in the previous study above, it could be caused by several factors, namely a long total ischemic time, changes in reperfusion strategies such as decreased use of primary PCI, inadequate health infrastructure, and concomitant infection with COVID-19.[13,19,25,26]

This study has a number of limitations, the first is that this study uses retrospective secondary data so that data collection is highly dependent on the accuracy and completeness of hospital medical records. Second, changes in examining COVID-19 status such as the use of antibodies, antigens or RT-PCR and changes in patient management policies during the COVID-19 pandemic era are very dynamic, depending on the number of cases of COVID-19 and the ability of hospital infrastructure to adapt to pandemic conditions and the availability of tools at the time. Third, our study did not include patients who died suddenly with suspected cardiac arrest which could suggest a longer onset before hospital admission. Fourth, not including the variable vaccine administration theoretically can provide external protection for sufferers of COVID-19. Fifth, this study was conducted in a single center, so the results cannot be generalized to STEMI patient populations elsewhere. Sixth, the observation time in this study was relatively short, namely only during hospitalization, so further research is needed to assess long-term outcomes.

CONCLUSION

This study shows that there is a decrease in patient admissions per month, a decrease in the use of primary PCI, an increase in the use of fibrinolytics and no reperfusion therapy, a prolonged onset and duration of total ischemic time, and a significant increase in major cardiovascular events in hospital in STEMI patients during the COVID-19 pandemic.

Public education regarding the importance of awareness of the signs and symptoms of STEMI, shortening the time for screening and antigen examination in the emergency room, increasing the availability of isolation catheterization room facilities, and improving the management of COVID-19 in general are expected to improve the morbidity and mortality of STEMI patients in the COVID-19 pandemic.

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Original Article

Correlation Procalcitonin (PCT) to Neutrophil Lymphocyte Ratio (NLR) in Covid-19 Patient

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Abstract

Background : Covid-19 treatment should be done early before the disease progress. Inflammatory biomarker is needed to ascertain the severity of disease as soon as possible. Neutrophil-to-lymphocyte ratio (NLR) and Procalcitonin (PCT) are two of biomarker that are clinically used around the world. NLR is simpler, can routinely be done and available in peripheral region while PCT is more effective to describe inflammation. This study aims to determine the correlation of procalcitonin (PCT) levels with neutrophil lymphocyte ratio (NLR) in COVID-19 patients.
Methods : This study is an analytic observational with a cross sectional design. We extracted data from medical record. Samples were 415 COVID-19 patients undergoing inpatient care at the Budhi Asih Hospital, East Jakarta for January - December 2021.
Results: Prevalence of male patients more than ≥60 years were 78 patients (18.8%) while female patients were 68 patients (16.4%). Average of PCT level was 1,93 ng/mL (0.02–200 ng/mL). Average of NLR was 5.09 cells/mm3 (0.22–31 cells/mm^3). Spearman test proved there was a significant correlation between PCT and NLR levels in COVID-19 patients (p value = 0.0001).
Conclusion: The higher the PCT level, the higher the NLR value in COVID-19 patients.

Keywords : COVID-19, Procalcitonin (PCT), Neutrophil Lymphocyte Ratio (NLR)

INTRODUCTION

Coronavirus Disease 2019 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. On March 11, 2020, WHO declared the phenomenon as a Public Health Emergency of International Concern (PHEIC) and a pandemic. In severe cases of COVID-19, it leads to an acute respiratory syndrome problem, pneumonia, kidney failure, and even to death.[1]

According to recommendation by WHO, gold standard of COVID-19 diagnosis is a biomolecular examination called real-time-PCR (qPCR). Samples in the form of RNA will be converted into cDNA in the form of a single strain and will be detected in real time.[2]

The presence of inflammatory in COVID-19 patients can be detected using procalcitonin (PCT) examination. PCT is a serological indicator in the shape of prohormones that are increasingly being studied for their role as a determinant of etiology in infectious diseases. Compared to other inflammatory parameters, such as CRP, PCT generally provides better sensitivity and specificity. After sensitization by bacterial stimuli, PCT levels also increase faster compared to CRP.[3]

In COVID-19 case, PCT help distinguishing between severe bacterial pneumonia and mild viral pneumonia. PCT level examination is an important test in identifying COVID-19 patients who are at high risk, have clinical aggravation, and patients with bacterial co-infection.[4] However, the PCT parameter has several disadvantages, such as high cost, long examination time, thus it is not widely available in health facilities in Indonesia.[5]

To detect inflammation in COVID-19 case, we also perform Neutrophil Lymphocyte Ratio (NLR) examination. Patients with severe SARS-CoV-2 infection are often characterized by neutrophilia that follows lymphopenia.[4] NLR is obtained from the comparison of neutrophil and lymphocytes.[6] Compared to PCT, NLR examination are easier to get, cheaper, non-invasive, and can be done more regularly.[7,8]

In previous studies, a similar analysis of PCT and NLR levels in Covid-19 case had been carried out. However, the study has limitation due to a small number of samples (n=5), so further research is needed on "Correlation of Procalcitonin Levels (PCT) with Neutrophil Lymphocyte (NLR) Ratio in COVID-19 Patients."

METHODS

This study was an analytical observational study with cross-sectional design. We collected data from medical records. This research was conducted in Budhi Asih Hospital in April–June 2022 and had been approved by ethic committee by issuing a letter number: 56/KEP-ETIK/III/2022. The samples were confirmed COVID-19 patients who admitted inpatient wards in the hospital with total sampling method. We performed analyzing using SPSS software. Spearman test was used to demonstrate correlation of PCT and NLR.

RESULTS

We collected 415 samples. The results showed most patients were male, older than 60 years old (Table 1).

Total average level of PCT was 1.93 ng/mL (0.02-200 ng/mL), while average level of NLR was 5.09 cells/mm^3 (0.22–31 cells/mm^3) (Table 2).

There were 73 (17.6%) patients with high NLR level and high PCT levels. Based on the results of the Spearman rank correlation analysis, with a confidence level of 95% ($\alpha = 0.05$), it was obtained p-value was equal to 0.0001, which meant a significant correlation between PCT and NLR levels (Table 3).

DISCUSSION

Our results showed that male, older than 60 years old (n=78; 18.8%) was more likely to undergo hospitalization compared to female in similar age group (n=68; 16.4%). Elderly patients experience a degenerative period causing decrease of immune response thus they will be more susceptible to infectious diseases and easily infected by SARS COV-2. In addition, female have more dominant immune system than male due to the influence of X chromosome, thus male might be more susceptible to COVID-19 than female.[9–12]

In this study, average PCT level was 1.93 ng / mL (0.02 ng / mL – 200 ng / mL). PCT level can reach up to more than 100 ng/mL in severe infection that manifest to clinical symptoms.[13] In viral infection, PCT shall not be induced as it is initiated by inflammation marker caused by bacterial infection. Increasing level of PCT was in line to severity of diseases.[14] The increase in PCT values occurs approximately 2 hours after exposure and sensitization of microbes. Peak PCT levels occur after 12–48 hours and then decrease.[15]

In this study, the average of NLR value was 5.09 cells/mm^3 (0,22 cells/mm^3 – 31 cells/mm^3). Inflammation caused by the virus resulted an increase in NLR level and induce worse symptoms.[16] Neutrophil work actively by migrating to immune system or organ.[17] Lymphocytes play a role in the process of maintaining homeostasis and inflammatory responses in the body. One of the characteristics of viral infection is occurrence of lymphopenia so that number of lymphocytes can be used as a reference index in the diagnosis of COVID-19 infection.[4,18] NLR is a combination of two parameters. An increase in neutrophil values indicates the presence of systemic inflammation while lymphopenia describes the sequestration of lymphocytes on the inflammatory site

TABLE 1
Respondents' Characterisitic based on Age and Gender

Variable		Gender				Total	
		Male		Female			
		n	%	n	%	n	%
Age (Years)	≥60	78	18.8	68	16.4	146	35.2
	50–59	60	14.5	58	14	118	28.4
	40–49	27	6.5	35	8.4	62	14.9
	30–39	30	7.2	22	5.3	52	12.5
	20–29	9	2.2	15	3.6	24	5.8
	6–19	5	1.2	6	1.4	11	2.7
	≤5	2	0.5	0	0	2	0.5
	Total	211	50.8	204	49.2	415	100

TABLE 2
Level of PCT and NLR

Variable	Average	Minimal	Maximal
PCT (ng/mL)	1.93	0.02	200
NLR (cells/mm^3)	5.09	0.22	31

TABLE 3
Cross Tabulation PCT and NLR

Variable		PCT level						p value
		High	%	Normal	%	Total	%	
NLR level	High	73	17,6	191	46	264	63.6	0.0001
	Normal	10	2,4	141	34	151	36.4	
Total		83	20	332	80	415	100	

and its apoptosis process.[19]

In this study, a positive correlation was found between PCT and NLR, which means both PCT and NLR could be used as an indicator of inflammation in COVID-19 case.[20,21] In line to Wang *et al*.[10,22] which stated there was a positive correlation between PCT and NLR in COVID-19 case. Xu *et al*. in their study found tendency of high level of PCR and NLR was simultaneously to severity and followed by other biomarkers such as CRP.[10] This suggested that NLR level was sufficient to represent inflammatory condition without the need for another biomarker examination, unless there was another indication.

In our study, there were 73 (17.6%) patients with high NLR level and high PCT level. These results were possibly due to inflammation response followed by bacterial co-infection. There were 191 (46%) case with high level of NLR and normal PCT level, this might be due to inflammation response in covid-19 without bacterial co-infection. Limitations of the study was there was no confirmation of bacterial co-infection. We suggested to enclose microbiological culture regarding this matter in the future study.

CONCLUSION

We found a significant correlation between procalcitonin (PCT) levels and ratio of neutrophil lymphocytes (NLR) in COVID-19 patients. The results of this study could be used as recommendations for clinicians in determining laboratory examination in COVID-19 patients.

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Original Article

Correlation Between Portal Venous Dimensions and Liver Stiffness in Patients of Child Pugh A Cirrhosis

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Abstract

BackgrLiver cirrhosis is an end-stage liver disease characterized by pathologic fibrosis and regenerative nodules with resultant liver dysfunction. The diagnostic hallmark of portal hypertension is slow flow velocities in addition to the increased caliber of the mean portal vein. That is, the diagnosis of portal hypertension requires the measurement of mean portal velocity and portal diameter, and the correlation between cirrhosis and mean portal velocity and port diameter is the correlation between liver cirrhosis and its complications. The objectives of this study was to analyze the correlation between portal vein dimensions and liver stiffness in patients of Child-Pugh A cirrhosis.
Methods : This study was a cross-sectional study on 30 subjects with Child-Pugh A liver cirrhosis. The subjects of this research are patients who come to the Radiology Department of the Dr. Kariadi Hospital in Semarang for point shear wave elastography and abdominal ultrasound examination from January to December 2022. Spearman test correlation was used for the analysis.
Results : Spearman test showed no correlation between liver stiffness and portal vein diameter (p=0.250, r= -0.217), liver stiffness and mean portal vein velocity (p=0.883, r= -0.028), and portal vein diameter with mean venous velocity in Child-Pugh A liver cirrhosis (p = 0.979, r = 0.005).

Keywords : Liver stiffness, portal vein diameter, portal vein velocity, child-pugh A

INTRODUCTION

Liver fibrosis develops as a reversible consequence of a sustained or repeated wound-healing response to liver injury caused by viral, toxic, and/or metabolic insults, and represents an imbalance between the synthesis and degeneration of the extracellular matrix. Accompanied by the distortion of hepatic structure and function, cirrhosis is the result of the progression of liver fibrosis. Liver cirrhosis is a fatal condition with a high fatality rate. The 12th leading cause of death in the US and the fifth leading cause of death for adults between the ages of 45 and 54 is cirrhosis and its consequences. According to the latest Global Burden of Disease Study, the global incidence of cirrhosis and other chronic liver diseases in 2017 was 5,154,900.[3] Moreover, from 2007 to 2017, the years lived with disability (or 'YLDs') and all-age deaths from cirrhosis have increased by 34.8% and 15.0% respectively. Hence, the clinical burden of cirrhosis is substantial. Even so, the advancement of liver cirrhosis can be stopped or slowed down with prompt and accurate screening and diagnosis.[1,14,15]

Biopsy and histopathological evaluation remain the golden standard for assessing liver fibrosis. However, this procedure is painful and has many complications including bleeding (0.3%) and death (0.01%). Hence, early recognition of patients with chronic liver disease (CLD) at high risk for developing its complication in a noninvasive manner is warranted to allow the implementation of optimal preventative management strategies that may modify the natural course of the disease. Cirrhosis itself, on the other hand, causes stiffening, prompting standardized cut-off value for its measurement. Cirrhosis is also known to lead to portal hypertension and metabolic liver failure. Cirrhosis causes intrahepatic portal hypertension secondary to increased hepatic venular resistance caused by intrahepatic fibrosis. The diagnostic hallmark of portal hypertension is slow flow velocities in addition to the increased caliber of the mean portal vein. That is, the diagnosis of portal hypertension requires the measurement of mean portal velocity and portal diameter, and the correlation between cirrhosis and mean portal velocity and port diameter is the correlation between liver cirrhosis and its complications.[14–17,19]

The purpose of this study is to evaluate the relationship between liver stiffness in patients with Child-Pugh A cirrhosis and the dimensions of the portal vein. The findings of this study are anticipated to serve as a foundation for the management and predictors of mortality in liver cirrhosis.

METHODS

This study employs a cross-sectional methodology. The liver stiffness variable was measured using point SWE using Acuson S2000 from Siemens at RSUP Dr. Kariadi at a specific time throughout the research's data collection period, which ran from July 2022 to August 2022. The ethical council of the Faculty of Medicine at Diponegoro University, Semarang approved the procedure (No.1097/EC/KEPK-RSDK/2022). The cross-sectional study design was used to determine the sample size. In the study of Hong *et al*., the correlation coefficient between the diameters of the portal vein and the stiffness of the liver is 0.5. The minimal sample size is 30 subjects according to the sample size calculation.[5]

The inclusion criteria in this study are age ≥18 years old, Child-Pugh A classification of liver cirrhosis, clinical cirrhosis of the liver, previous sonography showing features of liver cirrhosis and not with acute chronic liver failure, history of iron overload, biliary obstruction (primary sclerosing cholangitis and cholestasis), and passive congestion leading to congestive hepatopathy (congestive heart failure, congenital heart disease with pulmonary stenosis and tricuspid regurgitation). The exclusion criteria for study subjects are invalid readings from point SWE or portal hypertension which is unlikely for technical reasons.[18]

The patient fasted for 4–6 hours before the examination. The examination was performed with the patient in a supine or left lateral position with the arm. The measurement was made through the intercostal space as the best location for the acoustic window. The transducer was then positioned perpendicular to the liver capsule about 1–2 cm below the liver capsule to avoid reverberation artifacts. The optimal measurement depth is 4–5 cm from the skin layer. Region of Interest (ROI) should avoid major vessels, bile ducts, costal/rib shadows, and masses. The ROI area is about 1 cm^3. The examination was carried out in a neutral position. The patient was asked to take a deep breath and hold it. The examination was repeated ten times. The median value of the examinations was then used as the result of the elastography examination. The diameter of the inner wall (lumen) of the portal vein was measured in millimeters using sonography. Doppler sonography was used to calculate the mean highest and lowest velocity of portal vein blood flow in centimeters per second.

To prove the relationship between portal vein dimensions and liver stiffness, the authors also collected data regarding the subjects' age, sex, BMI, duration of illness, history of previous illness, history of alcohol consumption, and the subjects' previous laboratory test results. The formula used to prove the correlation will be Pearson if the data distribution is normal, or Rank-Spearman if one or both of them are not normally distributed.

RESULTS

In this study, 30 patients already classified with the Child-Pugh classification were chosen; consisting of 17 men (56.67 %) and 13 women (43.33 %). Two-thirds of the subjects were more than fifty years old (66.67%). Twenty-six of the samples (86.67%) have been ill for more than 24 months, two (6.67%) admitted to being ill for 1–6 months, and another two (6.67%) admitted to being ill for 7-12 months. Sixteen (53.3%) subjects were considered within the normal weight range (18.5–24.9 kg/m^2), and only three of the subjects were obese (30.0–34.9 kg/m^2).

Ten subjects (33.3%) had the result between 10–15 kPa when examined for liver stiffness, while 5 (16.67%) of them had the result of >30 kPa. Fourteen subjects' portal vein diameters were between 12–14 mm, while 3 subjects (10%) were <8 mm and another 3 were 10–12mm. Eighteen (60%) subjects were found with mean portal vein velocity between 15–30 cm/s, and only three (1-%) were found with >45 cm/s.

The results of the data normality test using the Shapiro-Wilk test showed that the liver stiffness variable, portal vein diameter, and mean portal vein velocity were not normally distributed (sig. > 0.05), leading Spearman to be used to analyze the correlation between the two variables.

The results of the Spearman test prove that there is no correlation between liver stiffness and portal vein diameter (p = 0.250, r = -0.217) and the mean portal vein velocity (p = 0.883, r = -0.028). There is no correlation between portal vein diameter and mean portal vein velocity with p = 0.979 and r = -0.005.

TABLE 1
Distribution of study sample based on gender, age, length of illness, BMI, liver stiffness, portal vein diameter and mean portal vein velocity

Variabel	Klasifikasi	N	%
Gender	Male	17	56.67
	Female	13	43.33
Age (years)	≤30	3	10
	31–50	8	26.7
	>50	19	63.3
Duration of illness (month)	1–6	2	6.67
	7–12	2	6.67
	13–18	–	–
	19–24	–	–
	>24	26	86.67
BMI (kg/m^2)	<18.5	5	16.67
	18.5–24.9	16	53.30
	25.0–29.9	6	20.00
	30.0–34.9	3	10.00
Liver stiffness (kPa)	10–15	10	33.3
	15–20	8	26.7
	20–25	3	10.0
	25–30	5	16.7
	>30	4	13.3
Portal vein diameter (mm)	<8	3	10.0
	8–10	6	20.0
	10–12	3	10.0
	12–14	14	46.7
	>14	4	13.3
Mean portal vein velocity (cm/s)	<15	4	13.33
	15–30	18	60.00
	30–45	5	16.67
	>45	3	10

DISCUSSION

All chronic liver diseases, whether toxic, hereditary, autoimmune, or infectious, undergo typical histologic changes, ultimately leading to fibrosis/cirrhosis and excessive matrix deposition. Cirrhosis rapidly decompensates and has a high mortality rate. Patients with cirrhosis have reduced liver capacity to metabolize and synthesize proteins, peptides, and hormones. In addition, fibrosis progression and nodal regeneration cause an increase in portal vascular resistance with portal hypertension and an increase in the hepatic venous pressure gradient (HVPG) of 0.10 mmHg. Portal hypertension eventually leads to ascites and the development of vascular collaterals such as esophageal varices. Portal hypertension finally leads to ascites, and vascular collaterals will develop such as esophageal varices. Signs of these clinical features are what we look for when classifying liver disease patients with Child-Pugh classification. Even so, the patients in our study were of Child-Pugh A, whose liver dysfunction is still compensated. This may be why none of our results shows a correlation with one another.[14]

Liver stiffness can be affected by confounding factors such as hepatitis, mechanic cholestasis, liver congestion, cellular infiltrations, and deposition of amyloid irrespective of fibrosis stage. Patients with cholestatic liver diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis, seem to have higher stiffness than those with viral hepatitis. Therefore, for each stage of fibrosis, cutoffs are higher than in chronic

TABLE 2
Spearmans test of liver stiffness, portal vein diameter, mean portal vein velocity

Spearman's rho		Liver stiffness	Portal vein diameter	Portal vein velocity
Liver stiffness	Correlation Coefficient	1.000	-.217	-.028
	Sig. (2-tailed)	.	.250	.883
	N	30	30	30
Portal vein diameter	Correlation Coefficient	-.217	1.000	.005
	Sig. (2-tailed)	.250	.	.979
	N	30	30	30
Portal vein velocity	Correlation Coefficient	-.028	.005	1.000
	Sig. (2-tailed)	.883	.979	.
	N	30	30	30

viral hepatitis either because of the nature of the liver disease or because of cholestasis. Similar higher cutoffs for each fibrosis stage were described in alcoholic liver disease. It should be mentioned that steatosis does not increase liver stiffness although it is often regarded as an essential initial state in chronic liver disease. Rather, steatosis may slightly decrease liver stiffness. As seen from our measurement data, our patients have varied levels of liver stiffness. This variety might affect the result of this research.[14,20]

Correlation between liver stiffness and the mean portal vein velocity

According to the Spearman test results, which were p=0.883 (p >0.05) and r = -0.028, there is no link between liver stiffness and the mean portal vein velocity. This is consistent with earlier research that linked liver stiffness to mean portal vein velocity such as Gunawan Y *et al.* (2022) which found no connection between liver stiffness and mean portal vein velocity and SWE. However, it disagreed with Sudirman I (2018), who demonstrated a weak correlation (r=0.271) between mean portal vein velocity as determined by ultrasonography and the degree of liver stiffness. Meanwhile, there is a significant correlation between the degree of fibrosis and the severity of fibrosis detected with SWE (p=0.001, r=0.672).[6,7]

Taking anti-hypertension medication may play a role. In this study, 4 of the subjects (10%) had been using propranolol for more than 3 months, and 15 (37.5%) had been using propranolol plus spironolactone. According to Amin *et al.* (2018), this can affect portal velocity in subjects because propranolol can lower portal pressure by reducing portal vein blood flow. This is associated with reduced cardiac output caused by the blockade of B1 adrenergic receptors.[8,9]

Correlation between liver stiffness and portal vein diameter

The results of this study showed no correlation between liver stiffness and portal vein diameter, measured at values of p=0.250 (p >0.05) and r = -0.217. This is consistent with previous studies that correlated the degree of hepatic stiffness with portal vein diameter, including Sudirman I (2018), which showed no significant relationship between portal vein di ameter and degree of hepatic stiffness (r = 0.166), but in contrast to Zaghloul S.G. (2019) who showed that changes in portal vein diameter are significantly correlated with liver stiffness.[6,10]

This may be due to several confounding factors beyond the investigator's control, such as the subjects' age and body weight. Ahmed M (2019) showed a significant correlation (r = 0.234; P=0.019 and r = 0.22; P=0.028) between portal vein diameter, age, and body weight, and Leao *et al.* (2012) showed that portal vein diameters were correlated significantly with age and BMI (p=0.02 and 0.001). Since the portal vein diameter rises with age with age and liver

Other variables that might affect the result are the level of subjects' ALT and the duration of their illness. An increase in portal vein diameter showed a statistically significant association with the duration of illness of more than six months (P <0.02) and increased serum alanine aminotransferase/ALT levels (P <0.03). Several studies have shown that increased aminotransferase levels are associated with higher shear wave velocity by virtual touch tissue quantification (VTQ) compared to that observed in patients with slightly elevated aminotransferases, which means that ALT serum level can also affect liver stiffness. The medication also played a part, as the mean portal vein diameter decreased significantly after 3 months of therapy with propranolol.

Propranolol is the most widely used non-selective beta blocker (NSBB) that causes a decrease in portal pressure due to reduced heart rate.[8,10,11]

Correlation between portal vein diameter and portal vein velocity

The results of this study showed that there is no correlation between portal vein diameter and mean portal vein velocity (p=0.979 (p >0.05) and r = 0.005). This is contrasting previous studies that show a correlation between portal vein diameter and the mean portal vein velocity, including Ahmed M (2019) (r=-0.628; P=0.0).[11]

Blood flow should be easier when there is no resistance, and velocity should be higher when the vein diameter is wider. This result might be influenced by previously mentioned factors that affect the portal vein. Further study might be necessary to confirm the hypothesis.

Limitations of the study

There were uncontrolled confounding factors in this study, including subjects' antihypertensive drug use (propranolol, bisoprolol, and spironolactone) over 3 months, age, BMI, disease duration, and serum ALT.

There are no cutoffs for liver stiffness grade, mean portal velocity, and portal diameter in this study because point SWE and ultrasonography are not the gold standards for diagnosis. Liver biopsy is the gold standard for assessing liver stiffness, but MR elastography is the best non-invasive method to assess liver stiffness. The gold standard test for portal hypertension is currently the HVPG.

CONCLUSION

This study proves that there is no correlation between portal vein dimensions and liver stiffness in patients with Child-Pugh A liver cirrhosis. Further research may be necessary with more controlled variables to confirm the hypothesis.

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Case Report

The Management of Deep Neck Abscess Comorbids with Kidney Failure

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Abstract

Background : Deep neck abscess is a life threatening disease as its complications. Some comorbidities affect the successful management of deep neck abscess. Kidney failure is one of comorbidities causing uremia which in turn affecting imbalance of pro and anti inflammatory mediators. This study was aimed to describe the proper management of deep neck abscess comorbids with kidney failure.
Case report : To report series of deep neck abscess comorbids with kidney failure being administered therapies with various outcomes.
Methods : Evidence based – literature review about deep neck abscess comorbids with kidney failure was conducted in *Pubmed, Clinical Key*, and *Google Scholar*. Retrieved articles were then critically appraised.
Results : Three evidence based-articles meeting criteria were included. The management of neck abscess comorbids with renal failure starts from kidney management according to Kidney disease: Improving Global Outcome (KDIGO) year 2012, and followed by management of deep neck abscess except in emergency situation. Diagnose and management of kidney disease need series examination of serume creatinine and urine monitoring.
Conclusion : The management of deep neck abscess comorbids with kidney failure commences with therapy for renal failure followed by management of deep neck abscess.

Keywords : deep neck abscess, kidney failure, comorbid

INTRODUCTION

Deep neck abscess is an abscess formed in a potential space in the deep neck.[1] A study by Chang *et al*. in Taiwan shows that of 127.283 patients with kidney failure, 280 patients experience deep neck abscess (0.1%).[2] In developing countries, incidence of deep neck absces is high. A study by Irmanto at Hasan Sadikin hospital in 2012 found 28 cases of deep neck abscess.[3] The successfull management of deep neck abscess is influenced by many factors involving diabetes melitus, hypertension, autoimune disease, and kidney failure.[2]

Severe inflammation worsens kidney impairment through pathophisiological processes including damage associated molecular pattern molecules (DAMPs)/ pathogen associated molecular patterns (PAMPs) recognized by immune cells, epithelial cells and parenchymal cells through interaction with receptors such as monocyte spreading and TLR-4 integrin expression forming reactive oxygen species (ROS) in basal cells. Increased ROS production and chemokine expression escalates proinflammatory activities from low density lipoprotein (LDL) and decreases anti inflammatory activities from high density lipoprotein (HDL) and endogenous antioxidants, anti inflammatory and cytoprotective system. Oxydative stress caused by substances or enzymes stimulated by inflammatory mediators induces apoptosis of endhotelial cells and kidney tubules.[4] This study aims to present case series of deep neck abscesses comorbid with kidney failure and to review its management from selected articles to foster understanding related to best management of deep neck abscess comorbids with renal failure.

CASE

We reported case series of deep neck abscesses comorbid with kidney failure undergoing therapies with various outcomes. Informed consents had been obtained from patients to presents medical record based-data in this report.

Case 1

A female patients aged 35 years presented with chief complaint of swollen neck accompanied by fever and breathless while lying down since 2 days before admission. Physical and medical examinations found bilateral submandibular abscess accompanied with bilateral parapharyngeal and retropharyngeal abscesses. Radiographic imaging of neck soft tissue shows radiopaque and radiolucent of minimaly multiple air at right colli until right supraclavicle suggesting a right colli abscess (Picture 1). Radiographic imaging shows bronchopneumonia dan cardiomegaly (Picture 2). Laboratory tests show kidney failure (ureum 281.4 mg/dL, and creatinine 10.12 mg/dL), controlled hypertension (averaged blood pressure 120/80 mmHg), leucocytosis (51000 cells/mm^3), and hypocalcemia (4.37 mg/dL).

Early management involves rehydration of cristalloid fluid and calcium gluconate in dextrose 5% to manage hypocalcemia followed by hemodialysis. Results show that ureum and creatinine decrease to 153.9 mg/dL and 5.09 mg/dL respectively.

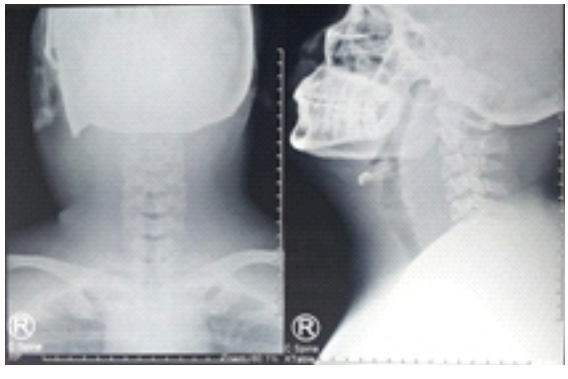
Subsequently, patients underwent incision and drainage of abscess under general anesthesia. A day after surgery, patient experienced fatigue, short of breath, and supraventricular, intercostal and subcostal retraction,

In intensive care unit, patients was put on a ventilator, and antibiotics of meropenem and levofloxacin were administered. A blood culture test was perfomed and patients was planned for urgent hemodialysis (ureum and creatinine level escalated to 300.4 mg/dL and 7.9 mg/dL respectively). However, patient experienced decreased consiousness level and was finally died.

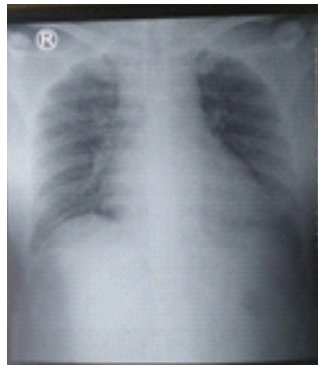
Case 2

A male patients aged 52 years presented with chief complaint of pain, swollen neck and painful swallowing. Patient had history of toothache 6 days before admission, fever and pus came out from the mouth.

Physical examination and imaging test show submental abscess along with right submandibular

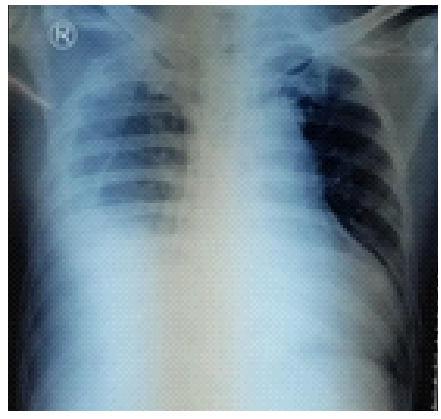


Picture 1. Radiographic imaging of neck soft tissue (Case 1)

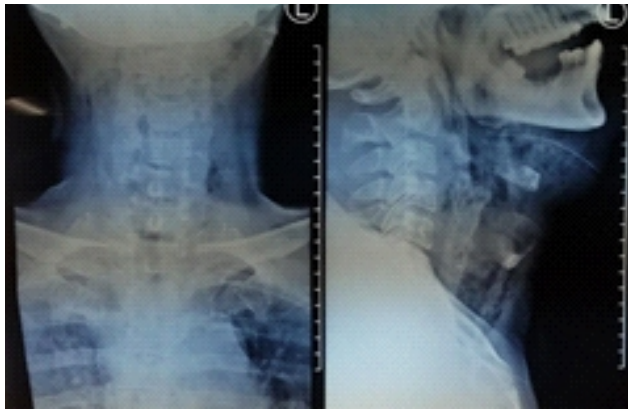


Picture 2. Thoracix X-ray (Case 1)

Picture 3. Next soft tissue X-ray (Case 2)



Picture 4. Chest X-ray (Case 2)



Picture 5. Neck soft tissue X-ray (Case 3)

abscess, parapharyngeal abscess, and retropharyngeal abscess. Neck soft tissue X-ray shows soft tissue mass and subcutaneous emphysema in submandibular and bilateral colli area caused by colli abscess (Picture 3).

Patient suffered from uncontrolled hypertension stage 2 (blood pressure 170/90 mmHg) and kidney failure (ureum 180.7 mg/dL and creatinine 1.87 mg/dL), suspected diabetes mellitus (random blood glucose 135 mg/dL), and airway obstruction grade 2.

Patient underwent tracheostomy under local anaesthesia followed by incision and drainage under general anaesthesia.

After surgery, patient was administered crystalloid fluids for rehydration therapy to manage kidney failure, and antibiotics (ceftriaxon and metronidazole), paracetamol and amlodipine oral to manage hypertension.

Patient experienced decreased consiousness level and transfered to ICU. Therapies involving switching antibiotic (meropenem), analgesics (morphine, paracetamol, and midazolam), omeprazole, tranexamic acid, vitamin K, nebulizer, N-Acetylcistein, and vasodilator (vascon) were administered to manage hypotension.

Patient's condition worsened on the fifth day in ICU and he was administerd therapies involving switching antibiotic (levofloxacine), dobutamine and norepinephrine to manage hypotension. Patient was planned for hemodialysis. However, his condition continously got worse and he went into cardiac arrest so cardiopulmonary resuscitation (CPR) was performed until patient was died.

Case 3

A male patient aged 50 years presented with left submandibular abscess and submental abscess spreading to left buccal, and suspected ruptured retropharyngeal abscess (Picture 5). Patients was referred from Department of Oral Sugery of Hasan Sadikin Hospital and had undergone incision and drainage of abscess.

Laboratory test shows kidney failure (ureum 243 mg/dL and creatinine 3,05 mg/dL). Subsequent management involves rehydration with cristalloid fluid, antibiotics (ceftriaxone and metronidazole), and analgesic (paracetamol) and tracheostomy to prevent aspiration.

Series laboratory test of serum creatinine was perfomed. On the fifth day of treatment, serum creatinine

declined significantly to normal and pus production is considerably decreased. Patient was discharged on the sixth day of treatment.

RESEARCH QUESTION

What is the proper management of patients with neck abscess comorbid with kidney failure?

METHODS

Literature search was conducted in Pubmed, Clinical Key, and Google Scholar using search terms of "deep neck abscess", "renal failure" and "therapy", synonims and related terms (Diagram 1). Subsequently, a critical appraisal (Table 1) was conducted. Checklist used for critical appraisal were retrieved from www.joannabriggs.com.

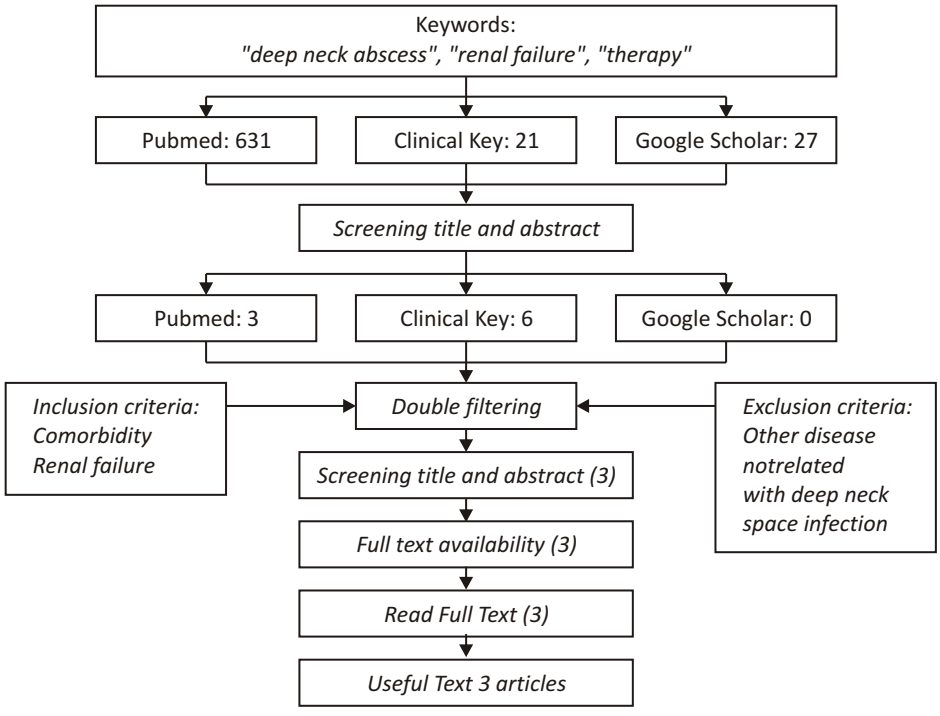


Diagram 1. Search flow chart

TABLE 1
Critical appraisal of three articles using the checklist

Checklist	Kurniawan et al.[16]	Novaldi et al.[5]	Chang et al.[2]
Patient's demographic characteristic is clearly described	-	-	+
Patient's history is clearly described and presented as timeline	+	+	-
Current clinical condition of patient is clearly described	+	+	-
Diagnostic tests or assessment methods and the results are clearly described	+	+	-
Interventions and treatment procedures are clearly described	+	+	+
Post-intervention clinical condition is clearly described	+	+	+
Adverse or unanticipated events are identified and described	-	-	+
The case report provide takeaway lessons	+	+	+
Level of Evidence*	5	5	5

Note: (+) yes , (-) no, (u) *unclear* ; **Level of Evidence* retrieved from *Centre of Evidence Based Medicine, University of Oxford*

RESULTS

Novialdi *et al*.[5] reported a case of submandibular abscess comorbid with uremia (ureum 101 mg/dL and creatinine 1,3 mg/dL) and old myocardial infarction among male patient aged 88 years.

Patient was administered antibiotics (ceftriaxone and metronidazole), anti inflammatory drug (dexamethasone) and underwent incision and drainage procedures under local anesthesia.

Kidney failure was managed with rehydration but conditions did not improve and got worse until patient was died.

Kurniawan *et al*.[6] reported upper airway obstruction caused by retropharyngeal abscess and sepsis induced by acute kidney failure in female patients aged 48 years.

Patient was hospitalised and administed cristalloid fluid rehydration, antibiotics (ceftriaxone and metronidazole), analgesic (ketorolac) and underwent incision and drainage of abscess. On the fifth day of treatment, patients was discharged.

The current management of kidney failure is based on KDIGO guidelines year 2012 involving fluid rescucitation, early antimicrobial therapy and infection control, vasopressor and inotropic agent to maintain tissue perfusion, and hemodialysis. As diagnostic markers and successfull therapy, series of laboratory tests of serum creatinine and urine output monitoring are performed.[7]

DISCUSSION

Deep neck abscess comorbids with kidney failure is still common. A study by Chang *et al*.[2] in Taiwan reported 280 of 127.283 kidney failure patients experience deep neck abscess (0.1%).

Early management involves rehydration therapy of cristalloid fluid, antibiotic, surgery and hemodialysis (the first and second cases). This is in line with KDIGO kidney failure management guidelines year 2012 involving fluid rescusitation, early antimicrobial therapy and infection control, vasopressor and inotropic agents, and hemodialysis.[7]

Fluid therapy is an important key to optimize hemodynamic of more severe kidney failure.[7]

Proper antimicrobial therapy along with infection control related to risk of worsened kidney failure and possibility of kidney recovery within 24 hours should be considered. Recommended antimicrobial therapy for kidney failure includes amikacin, meropenem, vancomycin, gentamicin, ciprofloxacin, cefepime, and clindamycin. The chosen antibiotics for the above three cases are ceftriaxone and metronidazole as empirical antibiotics for early management before the result of blood culture test are released and meropenem for patients with hemodialysis.[7]

In the first dan second cases, pasient were administered vasodilators to maintain adequate organ perfusion but unfortunately it is also influenced by many factors such as hypertension and suspected diabetes mellitus in the first and second cases. It is corroborated by a study by Chang *et al*.[2] explaining that deep neck abscess is influenced by comorbidities such as diabetes mellitus, hypertension, coronary heart failure, cerebrovascular insufficiency, and chronic obstructive pulmonary disease (COPD). The so many comorbidities influence the successful management of deep neck abscess.

In the first case, patient had bad prognosis. According to KDIGO criteria, patients is categorized in the grade 3 which may result in death.[7]

The KDIGO guidelines year 2012 recommends diagnosing and monitoring of the successful management of kidney failure based on serum creatinine and urine output monitoring. In the third case, patients was only monitored for its serum creatinine (and ureum), but urine output is not as a reference value for kidney failure management.[7]

In conclusion, kidney management is the first priority for deep neck abscess comorbids with kidney failure followed by management of deep neck abscess in hope that morbidity and mortality is avoided.

CONFLICT OF INTEREST

No conflict of interest during this study.

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Case Report

Thyroid Storm Post-Radioactive Iodine Therapy

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Abstract

Background : Thyroid storm is an endocrine disorder emergency which has a high morbidity and mortality rates. The incidence of thyroid storm is seen in less than 10% of all hospitalized thyrotoxicosis patients. However, it has a high mortality rate, which accounts to 20–30% of the cases. It is important to diagnose early to facilitate appropriate immediate management, which can improve prognosis and clinical outcome in patients. Thyroid storm usually begins with precipitating factor. Thyroid storm precipitated by radioactive iodine therapy is rare.

Case Report : We report a rare case in a 28 year old female patient. Patient came with complaints of palpitations, nausea without vomiting, fever, >3x diarrhea, and shortness of breath after radioactive iodine therapy. The clinical presentation of thyroid storm is polymorphic that becomes a diagnostic problem as it can delay treatment and increase the risk of mortality. It is important to suspect a thyroid storm based on the patient's clinical presentation, because the diagnosis of thyroid storm is based more on the patient's clinical presentation. The existence of the Burch-Wartofsky scoring system facilitates the diagnosis of a thyroid storm. The total Burch-Wartofsky score in this patient based on the clinical presentation is 45, which is highly suggestive of thyroid storm.

Conclusion : Thyroid storm precipitated by radioactive iodine therapy is rare. The incidence of thyroid storm after administration of radioactive iodine therapy is 0.34 percent. Precipitating factors other than the administration of radioactive iodine therapy such as infection and discontinuation of antithyroid drug therapy can trigger a thyroid storm.

Keywords : thyroid storm, emergency, post radioactive iodine therapy

INTRODUCTION

Thyroid storm is one of the fatal manifestation that occur in patients with thyrotoxicosis. The incidence of thyroid storm in all hospitalized patients with thyrotoxicosis is approximately 10%, but the mortality rate from thyroid storm is 20–30%. Thyroid storm often begins with precipitating factor related to a previous thyroid disease. Radioactive iodine has been used to treat hyperthyroidism since 1946 and the treatment of choice for the majority of thyrotoxic patients, which has been shown to be highly effective and safe.[1] Thyroid storm precipitated by radioactive iodine therapy are rarely reported, but when they do occur, they are serious and often fatal.

Prompt and appropriate intervention starting with a proper diagnosis can provide good outcomes in patients with thyroid storm. High vigilance and the ability to recognize thyroid storm is very helpful in preventing the onset of a thyroid storm. This case concerns a patient diagnosed with a diffuse toxic goiter with thyroid storm after radioactive iodine therapy.

CASE REPORTS

Female patient, 28 years old, came to the emergency room on October 27, 2021 at 17.00 WIB with complaints of increasing chest palpitations after radioactive iodine therapy. The patient have been diagnosed with hyperthyroidism since 5 months before. Patient complained nausea without vomiting, fever accompanied by toothache since the previous 2 days. Complaints were accompanied by diarrhea as much as >3x/day and shortness of breath. There were no loss of consciousness, cough with phlegm, or pain when urinating. Physical examination of the patient was as follow: moderate illness with compos mentis consciousness, blood pressure of 134/74 mmHg with regular pulse rate 154x/minute, respiratory rate 26x/minute, and temperature: 38.3°C. Exophthalmos in the eye and palpable diffuse enlargement of the thyroid gland in the neck was found. There was no increase in jugular venous pressure and no leg edema was seen in the patient. The results of the EKG examination showed sinus tachycardia and anteroseptal ischemia. The Burch-Wartofsky scoring system for the diagnosis of thyroid storm shows a total score of 45 points (Table 1), which supports highly suggestive thyroid storm diagnosis.

Laboratory investigations showed Hb levels of 11.6 g/dl (N=12.3–15.3), hematocrit 34.5% (N=36.0–45.0), erythrocytes 4.52 million/µL (N =4.5–5.1), leukocytes 16,540/uL (N=4400–11300) and platelets 220,000/uL (N=150,000-450,000), random blood sugar level 155 mg/dL (N = <140). Urinalysis results showed glucose +1 (N=negative). No bacteria were found on microscopic examination of urine and no amoebae or worm eggs were found on routine stool examination.

When arriving at the Nuclear Medicine Department, the patient came with complaints of palpitations, often feeling hot, losing weight dramatically in 1 year, defecating 4x/day, hair loss, hand tremors, emotional lability, difficulty sleeping, no regular menstruation, weak limbs, complaints of protruding eyes. There was no history of hypertension, diabetes, asthma or allergies. The patient routinely took Thyrozol 2x10 mg and propranolol 3x10 mg since 6 months ago, but stopped taking the medicine since 4 days ago. The patient brought laboratory results on July 23, 2021 showing thyroid hormone levels FT4 = 88.18 (N=9-20) and TSH = <0.05 (N=0.35–4.94). Then a re-check investigation of thyroid hormone levels was carried out at the Nuclear Medicine Department on October 25, 2021, showing TSH levels <0.0083 (N=0.55–4.94) and FT4 levels >5.00 (N=0.70–1.48). The patient received radioactive iodine therapy at the Department of Nuclear Medicine with a dose of 10 mCi of NaI–131.

The result of the thyroid scan in the Department of Nuclear Medicine showed a diffuse toxic goiter (Figure 1).

TABLE 1
Calculation Burch-Wartofsky scoring system for the diagnosis of thyroid storm in patients

Checklist		
Temperature	38.3°C	10
Tachycardia	154x/minute	25
Fibrillation	No	0
Congestive Heart Failure	No	0
Gastrointestinal Dysfunction	Diarrhoea, Nausea	10
CNS disorders	No	0
Triggers	Yes	10
Total Score		45

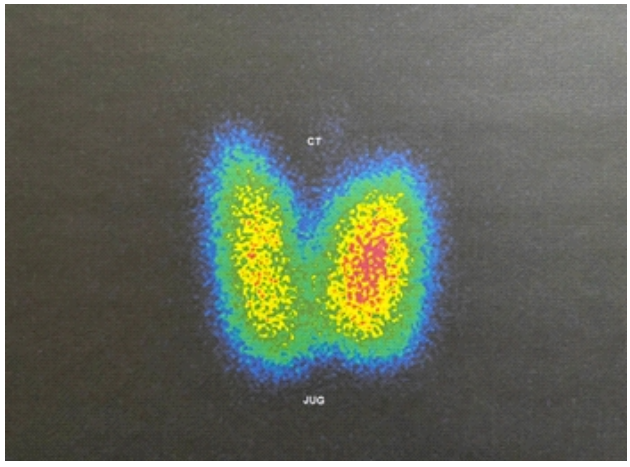

Figure 1.
Thyroid Scintigraphy Shows Diffuse Toxic Goiter

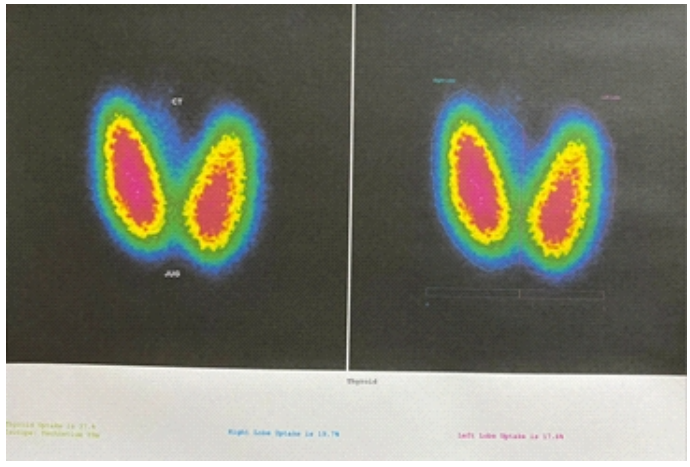

Figure 2.
Thyroid Uptake Test with a High Uptake Result

	Points		Points
Temperature °F (°C)		**Cardiovascular Dysfunction**	
99-99.9 (37.2–37.7)	5	Tachycardia bpm	
100-100.9 (37.8-38.2)	10	90-109	5
101-101.9 (38.3-38.8)	15	110-119	10
102-102.9 (38.9-39.4)	20	120-129	15
103-103.9 (39.4-39.9	25	130-139	20
≥104 (≥40)	30	>140	25
CNS Effects			
Absent	0	CHF	
Mild (agitation)	5	Absent	0
Moderate (delirium, psychosis)	10	Mild (pedal edema)	5
Severe (seizure, coma)	15	Moderate (bibasilar rales)	10
Gastrointestinal-hepatic dysfunction		Severe (pulmonary edema)	15
Absent	0		
Moderate (diarrhea, n/v, abd pain)	10	Atrial Fibrillation	
Severe (Jaundice)	20	Absent	0
Precipitating History		Present	10
Absent	0		
Present	10		

A score > 45 is highly suggestive of thyroid storm. Scores between 25-44 are suggestive of impending thyroid storm. A score <25 is unlikely thyroid storm.

Figure 3.
The Burch-Wartofsky scoring system for the diagnosis of thyroid storm

Figure 2 is the result of a thyroid uptake test in the Department of Nuclear Medicine, Hasan Sadikin Hospital, Bandung. The results of the uptake test value were 37% (the normal value of the thyroid uptake test at RSHS Bandung was 0.5–5%). The uptake value in the right lobe was 19.7%, while the uptake value in the left lobe was 17.6%.

DISCUSSION

Radioactive iodine has been used to treat hyperthyroidism since 1946. Since then, it was the treatment of choice for the majority of thyrotoxic patients, which has been shown to be highly effective and safe.[1] Thyroid storm precipitated by radioactive iodine therapy are rarely reported, but when they do occur, they are serious events and often fatal.

The clinical presentation of thyroid storm is sometimes polymorphic and becomes a diagnostic problem that can delay treatment and increase the risk of mortality. It is important to suspect a thyroid storm based on the patient's clinical presentation, as the diagnosis of thyroid storm is based more on the clinical presentation rather than laboratory test results. The existence of the Burch-Wartofsky scoring system could facilitate the diagnosis of a thyroid storm.[2-5] In this patient, a total score of 45 points (Table 1) supports a highly suggestive thyroid storm diagnosis.

TABLE 2
Studies with Large Number of Hyperthyroid Patients Treated with Radioactive Iodine

Study	Patients Treated with Radioiodine	Cases of Thyroid Storm	Severe Exacerbations
Nicholson *et al.* [22]	136	1	0
Christensen *et al.* [23]	50	1	0
Feitelberg *et al.* [24]	184	1	0
Rubenfeld *et al.* [25]	294	1	0
Nadler *et al.* [26]	86	1	0
Beierwaltes and Johnson [27]	330	4	10
Werner *et al.* [28]	525	1	6
Williams *et al.* [30]	111	0	3
Larsson [31]	370	0	2
Davis and Davis [32]	81	0	5
Cassidy and Astwood [34]	465	0	0
Chapman *et al.* [35]	343	0	0
Total	2.975	10 (0.34%)	26 (0.88%)

TABLE 3
Factors Precipitating Thyroid Storm

Several conditions have been reported to cause thyroid storm	
Thyroid gland surgery	Radioactive iodine therapy
Non thyroid surgery	Iodine contrast exposure
Traumatized	Discontinuation of antithyroid therapy
Excessive manipulation of the thyroid gland	Untreated Graves' disease
Thyroiditis	Infection
Labor	Hypoglycemia
Burns	Thyroid cancer metastases
Myocardial infarction	Molar pregnancy
Pulmonary embolism	Psychological stress
CVA	Strenuous physical activity
Drugs: anesthetics, salicylates, pseudoephedrine, and amiodarone	

Based on the literature, the pathophysiology of thyroid storm after administration of radioactive iodine (I–131) causes injury to thyroid follicular cells, which acutely releasing stored thyroid hormone into the circulation. Histopathological examination of the thyroid gland in the first two weeks after administration of radioactive iodine has shown epithelial swelling and necrosis, disruption of follicular structure, edema, and infiltration of polymorphonuclear leukocytes. Another study demonstrated a statistically significant increase in triiodothyronine and thyroxine levels 24 to 48 hours after administration of therapeutic doses of I–131 to a group of

hyperthyroid patients. This corresponds to the marked elevation in thyroid function test results found by Mazzaferri and Skillman. Free thyroid hormone levels are markedly increased in patients with thyroid storm compared to the uncomplicated group, possibly as a result of an acute decrease in thyroid-binding protein. How this mechanism relates to radioactive iodine-induced thyroid storm and other complications remains unclear. It should also be noted that other events, such as discontinuation of antithyroid drugs and violent palpation of the thyroid gland, both common at the time of administration of I–131, were also reported in previous studies to be precipitating factors in cases of thyroid storm. It is possible that this event may have been important, or at least contributed, to the development of subsequent complications radioactive iodine treatment that can not be ignored.[6,7]

Thyroid storm is a quite rare medical emergency, still unfamiliar and often overlooked by clinicians. Several other studies reported that out of 2,975 patients who were given radioactive iodine therapy, thyroid storm was reported in 10 patients (0.34 percent), while 26 patients (0.88 percent) were said to have experienced moderate exacerbations of thyrotoxic symptoms.

Thyroid storm triggers such as infection, stress, myocardial infarction, or trauma will amplify the effects of thyroid hormone by freeing thyroid hormone from its binding sites or increasing receptor sensitivity in tissues through upregulation of adrenergic target cell receptors or postreceptor modifications in signaling pathways.

Thyroid storm and severe exacerbations of thyrotoxicosis associated with I–131 treatment are rare, but must be kept in mind because of the high mortality rate. It is important to identify patients at risk before implementing preventive measures. High-risk patients include elderly, severe thyrotoxicosis, significant weight loss, and those with cardiovascular or cerebrovascular disease. The risk is lower in patients with other chronic diseases, such as diabetes mellitus and peptic ulcer disease, as well as those with severe dehydration and infection. Patients with very large goiter, multi-nodular goiter, and prolonged thyrotoxicosis are also a high-risk group. Several other conditions that can trigger a thyroid storm are presented in Table 3.[8-10]

Infection is one of the causes of fever, which can also trigger a thyroid storm. Infection is proven to be the most common precipitating factor for thyroid storm with an incidence rate of 28%.

The precipitating factor in this patient is the presence of infection on the teeth, which is consistent with a very high level of leukocytes i.e. 16.540/uL, while the normal level of leukocytes is between 4400–11300/uL. Based on the ATA guidelines in the diagnosis and management of hyperthyroid and thyrotoxicosis patients, patients at high risk for thyroid storm (patients with free T4 levels 2–3 times normal) are recommended to be administered methimazole and carbimazole antithyroid drugs as premedication. Discontinuation of antithyroid drugs before giving radioactive iodine therapy can also be a precipitating factor for thyroid storm.

Thyroid storm is usually be triggered by precipitating factors previously stated. In this case, it was also triggered by non-adherence to the treatment program, in which radioactive iodine therapy is initiated without proper preparation. Preparation before radioactive iodine therapy include stopping drugs or foods containing high iodine level at least 1 week in advance, stopping antithyroid drugs at least 5 days before. On the day of radioactive iodine administration, the patient must fast and may only eat one hour after administration of radioactive iodine therapy.

Several side effects that need to be considered after radioactive iodine therapy include exacerbation of thyrotoxicosis to thyroid storm. However, these side effects are rare. After 1 week follow-up post radioactive iodine therapy, dry mouth and swelling sensation on thyroid area usually has gone away on its own. Hypothyroidism that occurs after treatment can be transient (usually 3–6 months after treatment) or persistent (monitored by checking TSHs levels periodically every 3–6 months). The risk of hypothyroidism after radioactive iodine therapy with moderate doses is approximately 10% within the first 2 years, and approximately 3% each year thereafter. The higher the dose given, the earlier the occurrence and the higher the incidence of hypothyroidism. Treatment of hyperthyroidism with radioactive iodine is preferred in patients who are resistant to antithyroid drugs or have recurrent hyperthyroidism after thyroidectomy. There is no age limit for those who are allowed to receive this method of treatment as it has been proven not to interfere with fertility, and has no teratogenic, carcinogenic or leucomogenic effects. Thyroid storm after radioactive iodine therapy will occur due to the sudden leakage of thyroid cells. This condition needs to be protected with corticosteroids 1 week before RAI.[8-10]

CONCLUSION

Thyroid storm precipitated by radioactive iodine therapy is rare. The incidence of thyroid storm after administration of radioactive iodine therapy is 0.34 percent. The presence of precipitating factors other than the administration of radioactive iodine therapy, such as infection and discontinuation of antithyroid drug therapy, can precipitate the thyroid storm.

CONFLICT OF INTEREST

There is no conflict of interest.

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Case Report

Platelet-Rich Plasma (PRP) as A New Approach and Promising Therapy in Patients with Alopecia Areata

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Abstract

Background : Alopecia areata (AA) is a non-scarring, autoimmune, inflammatory condition that causes well-defined areas of hair loss on the scalp and/or body. A new biotechnology called platelet-rich plasma (PRP) was developed as a result of increased interest in tissue engineering and cell-based therapies. This therapy is defined as an autologous, non-allergic preparation of platelets in concentrated plasma. Study aimed to evaluate the effect of PRP treatment in alopecia areata.
Case : This study included 3 patients complaining of multiple patchy alopecia areata. They were treated with combination of PRP therapy, topical fluocinolone acetonide 0.025% cream, minoxidil 2 and 5%, and ketoconazole 2% scalp solution. One patient was also treated with intralesional triamcinolone acetonide injections. PRP was injected intradermally every 4 weeks and final monitoring was conducted after 4–6 sessions. Evaluation and follow up results were determined using photographic monitoring as well as patient's satisfaction.
Results : Administration of autologous PRP had significance hair regrowth in all three patients in this study. PRP treatment sessions varied from 3 to 6 sessions. However, significance outcomes in these patients were established after 3 sessions of PRP treatment, while the best results were obtained after 4-6 sessions of PRP treatment. No major side effects was reported.
Conclusion : PRP is effective in promoting hair growth. PRP treatment for alopecia areata is safe, easy to perform, and can achieve patient's satisfaction, without any major adverse effects. However, further research on standardized protocol of PRP methods are needed.

Keywords : platelet-rich plasma, alopecia areata, hair loss

INTRODUCTION

Alopecia areata (AA) is a non-scarring, autoimmune, inflammatory condition that causes well-defined areas of hair loss on the scalp and/or body. It is still unclear how AA develops from a pathogenic standpoint. Recently, the pathomechanism of AA has been thought to be an organ-specific autoimmune disease and it can cause inflammation that induce hair loss. In severe situations, hair loss can lead to total body baldness (alopecia universalis) or full loss of hair from the scalp (alopecia totalis). The majority of therapy for AA are immunosuppressive because it is thought of as an organ-specific autoimmune disease, yet up until now, AA has been difficult to treat.[1,2] A new biotechnology called platelet-rich plasma (PRP) was developed as a result of increased interest in tissue engineering and cell-based therapies.[3] This therapy is defined as an autologous, non-allergic preparation of platelets in concentrated plasma from the patient's own blood.[1] PRP contains a variety of cytokines and growth factors that improve the body's ability to repair and regenerate.[3] PRP has been beneficial in dermatology, particularly in acne scars, hair regrowth, wound healing, and fat grafting.[3]

Typical blood sample consists of 93% red blood cells (RBCs), 6% platelet, and 1% white blood cells (WBCs), but in PRP, the platelet concentration is enriched through centrifugation. The concentration of platelets is 94% and the concentration of RBCs is 5%.[3] Thus, the concentration of platelets is 4-7 times above baseline values.[2] PRP contains high concentrations of over 20 different growth factors, that can enhance recruitment of reparative cells in hair loss although the exact mechanisms are still unknown. The aim of this study is to evaluate the efficacy and safety of PRP treatment in alopecia areata.[2]

CASE REPORTS

In this study, we evaluated the effectiveness of PRP treatment for alopecia in 3 patients. This study was conducted from October 2020 until April 2021 at Gardenia Clinic, Dr. Kariadi General Hospital, Semarang. All patients gave a written informed consent. One session of PRP treatment was repeated every 4 weeks and final monitoring lasted after 5–6 sessions. Evaluation on subject's hair growth was performed in every session of treatment by photographic monitoring. The patient's satisfaction and evaluation of clinical improvement, including hair counts/density, hair thickness, and general alopecia photographic monitoring, are made easier with a follow-up period that is sufficient.

The production and delivery of PRP followed a very wide range of methods. In this investigation, we prepared PRP using a double-spin centrifugation procedure. In the laboratory, 30 mL of patient's blood was taken. We used 3 sterile 15 mL conical falcon tubes, each containing 1.4 mL citrate phosphate dextrose (CPD), and then we added 10 mL of the patient's venous blood to each sterile conical falcon tubes and homogenized them. Double-spin centrifugation involved first spin being at 100 g for 6–10 minutes and the second spin being at 400 g for 10–15 minutes. Three layers were formed after the first spin, namely the top layer was acellular plasma (platelet-poor plasma), the middle layer was buffy coat, and the bottom layer was red blood cells. We transferred the platelet-poor plasma and buffy coat into a new sterile conical falcon tube without anticoagulant. Two layers were formed after the second spin, namely the upper layer was platelet-poor plasma and the lower layer was platelet-rich plasma (PRP) (1 mL). Platelets would be activated to produce growth factors and cytokines with the application of an activator called calcium gluconate. A

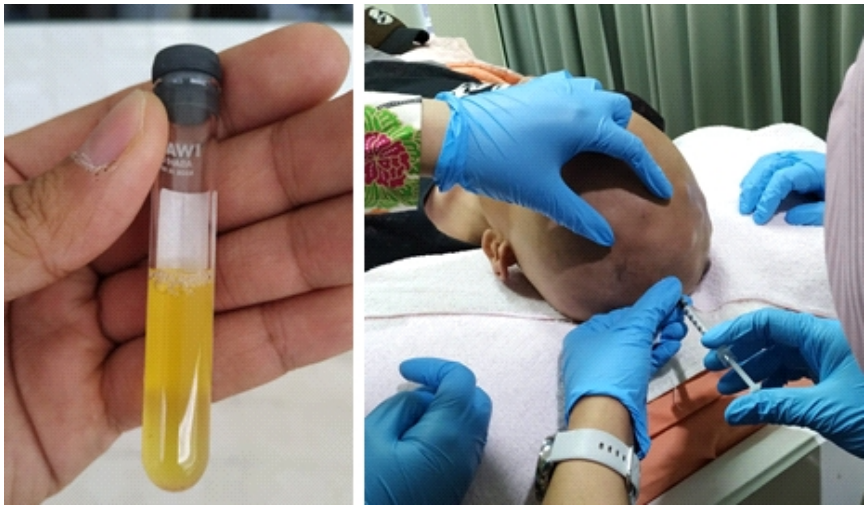

Figure 1. (a) An average volume of pure PRP obtained after double-spin centrifugation, **(b)** Intradermal PRP injections in scalp areas using the nappage technique.

Figure 2. Progress of PRP treatment in patient with alopecia totalis.
The patient improved markedly within 5 sessions of treatment

typical volume of 2 ml of pure PRP was used for the entire amount of PRP injected (Figure 1a).

Before injection, topical anesthetic was needed for 30 to 60 minutes using topical lidocaine 2%. A linear pattern of numerous tiny injections spaced 1 cm apart should be used to apply intradermal injections at a rate of roughly 0.1 ml/cm^2 to specific scalp locations. The depth should be between 1.5 and 2.5 mm (Figure 1b).

Case 1

The main complaint of a 17-year-old male patient was asymptomatic scalp hair loss for the previous five years. The baldness on his head began as a small patch of hair loss that steadily grew larger until it covered his entire scalp. There was no familial history of the condition, no drug use history, and no signs of a systemic illness. Examining the region revealed a large and well-defined balding patch. The area was smooth and showed no signs of skin alterations. The patient was diagnosed with alopecia totalis and treated with a combination of PRP and intralesional triamcinolone acetonide injections (5 mg/ml) every 4 weeks, alongside daily application of topical fluocinolone acetonide 0.025% cream twice daily, minoxidil 5% spray twice daily, and ketoconazole 2% scalp solution once every two days. The patient improved markedly within 5 sessions of treatment (Figure 2).

Case 2

The main complaint of a 18-year-old female patient was asymptomatic scalp hair loss for two years. There was no family history of the illness, nor was there any drug use or trauma. Upon investigation, there was no evidence of autoimmune illness. At the parietal and occipital regions of the scalp, there was alopecia without scarring. Systemic analysis was normal. The patient was diagnosed with alopecia areata. PRP injections was conducted every 4 weeks alongside daily application of topical fluocinolone acetonide 0.025% cream twice daily, minoxidil 2% spray twice daily, and ketoconazole 2% scalp solution once every two days. Remarkable improvement was shown after 12 weeks, while the best result was obtained after 4 sessions of treatment (Figure 3).

Case 3

The main complaint of a 19-year-old female patient was asymptomatic scalp hair loss since the beginning of October 2019. The patient made the decision to cut all of her hair after the hair loss progressed from a little spot on the right and left sides of the scalp to bald patches on both sides. Additionally, the patient reported suffering from shoulder joint pain. There was no family history of the condition. On physical examination, there was non-scarring alopecia at frontoparietal, both temporal, and occipital regions of scalp, there was no malar rash, there was pain and limited range of motion of the shoulder joints, and the other organ systems were within normal limits. On laboratory examination, anti-PM Scl100 in ANA profile was borderline positive, antinuclear antibody (ANA), and anti DsDNA were negative. There was vitamin D deficiency. The patient was diagnosed with alopecia areata and rheumatoid arthritis. The patient was treated with a combination of PRP injection every 4 weeks, application of topical fluocinolone acetonide 0.025% cream twice daily, minoxidil 2% spray twice daily, and ketoconazole 2% scalp solution once

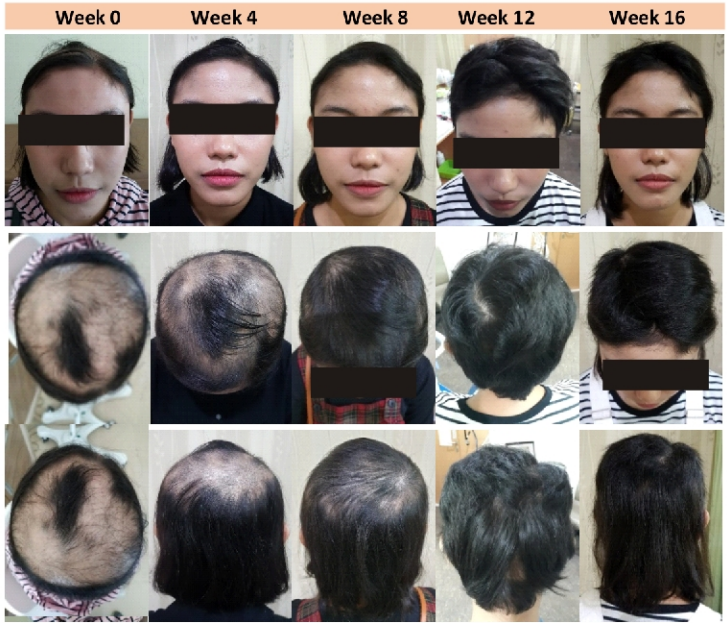

Figure 3. Progress of PRP treatment in patient with alopecia areata.
Remarkable improvement was shown after 12 weeks, while the best result was obtained after 4 sessions of treatment

every two days. Patient was also treated by internal medicine specialist with oral prednisone 5 mg/12 hours, cyclosporine 25 mg/day, and calcitriol 1 tablet/day for rheumatoid arthritis. Remarkable improvement was shown after 3 sesions of treatment, which was 12 weeks (Figure 4).

DISCUSSION

Alopecia areata (AA) is a chronic organ-specific disease that affects hair follicles and sometimes nails. According to statistics, 0.2% of population have an AA episode at some point in their lives, and 1.7% of population will have one overall. Although the exact etiopathogenesis is unknown, autoreactive T lymphocytes that target the hair follicles are likely to be a mediator.[4]

Alopecia areata (AA) can develop into alopecia totalis, which affects the entire scalp, and alopecia universalis, which affects the hair on all other body parts. The treatment suggestions are primarily based on case series and clinical experience because there are so few randomized trials and available data for treatment methods. Patient counseling regarding the nature of the disease is crucial. Alopecia areata is frequently treated with topical corticosteroids, as well as occasionally with occlusion. Other therapeutic options include oral corticosteroids, intralesional triamcinolone acetonide (5–10 mg/ml), and hydrocortisone acetate (25 mg/ml). For wider areas, contact immunotherapy using dinitrochlorobenzene, squaric acid dibutylester, and diphenylcyclopropenone has been suggested with varying degrees of success. Other treatment options include photochemotherapy, topical minoxidil administration, and use of dithranol.[4]

Because of the inflammatory process in alopecia areata, corticosteroids have been the most commonly used treatment modality and have good efficacy in hair regrowth. Several forms of topical corticosteroids have been used in AA, such as fluocinolone acetonide gel, fluocinolone scalp cream, betamethasone valerate lotion, and clobetasol propionate ointment.[5] They are painless and safe. Folliculitis is a frequent adverse reaction to corticosteroid therapy.[5,6] In this patient, we used fluocinolon acetonide 0.025% cream twice daily.

The local impact of topical corticosteroids is the strongest, and systemic adverse effects are the least. Immunosuppression and a decrease in local inflammation near the dermal papilla are the key mechanisms of action. Additionally, corticosteroids block the T-cell-mediated immune response that affects the hair follicles.[7] Corticosteroids administered intralesionally are frequently used to treat AA. When diseases are localized and affect less than 50% of the scalp, they are the primary line of treatment. Commonly used steroids include triamcinolone acetonide (5–10 mg/ml) and hydrocortisone acetate (25 mg/ml). We used triamcinolone acetonide 5 mg/ml intradermally to this patient. Typically, a 30-gauge needle and a 1 ml syringe are used to give triamcinolone acetonide at a dosage of 5 mg/ml through a series of 0.1 ml injections spaced 1 cm apart. A maximum of 3 ml of the solution is injected intradermally on the scalp during a single visit, in or just

Figure 4. Progress of PRP treatment in patient with alopecia areata.
Remarkable improvement was shown after 12 weeks (after 3 sessions of treatment)

beneath the dermis. In responding patients, hair regrowth often appears within 4–6 weeks.[6]

Minoxidil was originally made as an antihypertensive medication and hypertrichosis was one of its most common side effects.[8] Minoxidil then was developed to treat male and female pattern alopecia, which can stimulate hair growth and reduce hair loss. In addition to vasodilatation, dermal papilla and follicular cells are stimulated by minoxidil, directly promoting hair growth.[9] Additionally, minoxidil can accelerate the transition to the anagen phase and also shorten the telogen phase to 1 to 2 days by increasing DNA synthesis in anagen bulbs, stimulating follicular proliferation and differentiation, and causes a rapid shift to the anagen phase by inducing β-catenin activity. Minoxidil also stimulates the production of prostaglandin E2, the most upregulated target gene in the β-catenin pathway in dermal papilla cells, to keep hair follicles growing continuously and maintaining the anagen phase.[8] In conclusion, the vasodilatation, potassium channel opening, anti-androgen, angiogenesis, the release of growth factors, stimulation of dermal papilla, and immunosuppression are the postulated mechanisms of action for minoxidil. Topical minoxidil comes in two concentrations, 2% for women and 5% for men, and is available as a spray and a foam. For best effects, apply it twice daily for at least 4 hours.[7]

Ketoconazole is an imidazole antifungal. Topical ketoconazole stimulates hair growth significantly. Actually, topical ketoconazole has more effects on androgenic alopecia because of its antiandrogenic properties. However, topical ketoconazole also has anti-inflammatory properties, so it can also be used in alopecia areata.[7,10]

A novel medical procedure called platelet-rich plasma (PRP) therapy is frequently used to regrow hair, especially in cases of androgenic alopecia and alopecia areata.[7] An autologous preparation of concentrated platelets in plasma is called platelet-rich plasma (PRP). Over 20 distinct growth factors have been found in PRP.[2] Multiple growth factors, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and interleukin-1 are released by platelet alpha-granules after activation.[2,7,11] These growth factors are widely known for causing the proliferative phase, transdifferentiation, and creation of new follicular units in hair and stem cells.[2] PRP increases the creation of new follicles, neo-vascularization, and angiogenesis by acting on stem cells

in the bulge area.[7]

Our research demonstrated that PRP had a strong local effect on AA regardless of gender or the length or course of the disease. Given the significant inflammatory process that distinguishes AA, it's feasible that PRP's anti-inflammatory properties could be helpful in this condition.[2]

None of the aforementioned trials found any significant negative effects, such as scarring, gradual deterioration, or infections. Notably, the side effects observed were negligible. The pain was bearable. After treatment or the end of the sessions, no analgesics were required. After receiving PRP treatment, no patients reported any erythema or soreness. PRP is risk-free, simple to execute, has few side effects, and causes no downtime at all.[1]

The use of autologous PRP as a therapy option for AA is possible. It is risk-free and very effective at regrowing hair.[2] The number of treatment sessions ranged from three to six. After three PRP therapy sessions, however, meaningful outcomes in these participants were determined. In order to monitor hair loss and determine whether further PRP treatments are necessary, it's crucial to follow patients for at least 12 months.

Because hair loss in men and women can have different symptoms and different mechanisms, it may be inappropriate to extrapolate the results to both genders in studies investigating only one gender. Our study has some limitations, including the relatively small sample size and the absence of more impartial methods of evaluation (videomicroscopy or trichoscopy).

CONCLUSION

Based on our evaluation of the therapeutic efficacy of PRP treatment for alopecia in three subjects, we draw the conclusion that PRP was successful in promoting hair growth. Before PRP is widely used as a therapy option in the clinical setting, a number of research design issues need to be resolved, even if our work shows PRP as a possible treatment option for alopecia. The requirement for repeat treatments, consistent objective data documentation and evaluation, physician and subject assessment, and isolating the effects of PRP in various grades and types of alopecia should all be determined through further research. Although 3–4 treatments of PRP injections with 4 weeks apart showed positive benefits in this study, a minimum of 5 sessions of therapy are advised for optimal results.

Documenting patient satisfaction and self-reported results might be helpful in identifying PRP treatments that are successful as well as those that will lead to high compliance because patient satisfaction is currently a key focus in health systems.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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Case Report

Serial Case: Infarct Stroke In Covid 19 Patients

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Abstract

Background : SARS-CoV-2 has been reported to cause various neurological symptoms including stroke. SARS-CoV-2 infection causes the release of cytokines, proinflammatory chemokines, immune system activation, coagulopathy, endothelium, vasculitis, hypoxia, renin-angiotensin system imbalance, and cardiovascular complications, all of which can contribute to stroke. The purpose of this study was to describe the incidence of stroke with different conditions in COVID 19.
Cases : There were two cases of stroke infarct in a COVID-19 patient who was admitted to our hospital. Both were treated with a diagnosis of stroke infarct with previous COVID-19 symptoms, the results of laboratory examinations revealed an increase in inflammatory markers in both patients and had been given appropriate treatment according to each patient's condition. But at the end of the treatment one patient died and the other patient went home with clinical improvement.
Discussion: The incidence of stroke infarct in this case is thought to be due to several factors, namely the presence of comorbidities in the patient, microvascular thrombus due to the formation of neutrophil extracellular traps (NET), activation of complement which causes thrombogenesis and vasculopathy, formation of antiphospholipid antibodies so that protein c is reduced, the formation of microparticles causes platelet hyperactivation. and increased tissue factor (TF) resulting in hypercoagulation. Adequate therapy in controlling inflammation due to COVID 19 has shown clinical improvement in stroke infarct patients.
Conclusion : There are 2 cases of stroke infarction in patients with covid 19 who have comorbidities. The first case with COVID advanced stages experienced a worsening of the condition despite being given appropriate therapy. The second case with COVID middle stages experienced an improvement in the condition after the viral inflammatory factors were controlled and the comorbidity was well controlled.

Keywords : Stroke infarction, COVID 19, SARS-CoV-2, Hypercoagulation, Vasculopathy

INTRODUCTION

Stroke is a syndrome characterized by rapidly developing clinical symptoms and/or signs in the form of focal and global brain functional disturbances lasting more than 24 hours, which are not caused by other causes other than vascular causes.[1] As a member of the coronavirus family, SARS-CoV -2 is an RNA virus that shows genetic similarity to SARS-CoV-1 and MERS-CoV.[2] In a study of 17,799 hospitalized patients with SARS-CoV-2 infection, a stroke risk of 0.9% was found with ischemic stroke occurring in 79% of patients, hemorrhagic stroke in 17%, and 4% had cerebral venous thrombosis.[3,4] Invasion of SARS-CoV-2 to the central nervous system (CNS) can be via neuronal, lymphogenous and haematogenous routes. SARS-CoV-2 infection causes the release of cytokines, proinflammatory chemokines, activation of the immune system, coagulopathy, endotheliitis, vasculitis, hypoxia, imbalance of the renin-angiotensin system, and cardiovascular complications, all of which can lead to stroke.[5,6]

Critically ill patients, those with previous co-morbidities and patients taking certain drugs such as drugs with a high risk for arrhythmias or thrombophilia will be more susceptible to stroke after SARS-CoV-2 infection.[6] Strokes in patients infected with SARS-CoV-2 are reported to have its distinctive features include occurring in young patients (mean age <55 years) without classic vascular risk factors, with a high prevalence of cryptogenic stroke and an increased incidence of large vessel stroke, even in patients with mild SARS-CoV-2 infection.[7] This case report will discuss the incidence of stroke infarction in COVID 19 patients.

CASE REPORT

Case 1

A 48 year old woman came with complaints of 3 days of SMRS fever and cough, 2 hours of SMRS the patient could not be awakened by the family, only responding with painful stimuli. While in the emergency room, the patient's consciousness improved (fully conscious), left limbs weak, could only resist light resistance, lips drooped to the right, slurred speech, headache, fever, cough and shortness of breath. She denied past medical history such as previous stroke, hypertension, diabetes mellitus, heart disease, high cholesterol. Previously denied contact history with COVID-19 sufferers, the patient had received the COVID-19 vaccination.

Physical examination revealed GCS E4M6V5, blood pressure 130/80 mmHg, pulse 80x/minute, respiratory rate 24x/minute, temperature 37.30C, SpO2 97% with O2 NRM 10 lpm. Neurologic status : central left VII and XII cranial nerve paresis, left spastic hemiparesis (strength 555/444 555/444). The results of supporting examinations were obtained:

Leukositosis	17.200/Ul,
Increase CRP level	2.07 mg/dl
Increase feritin level	1809.4 ng/ml
Increase D Dimer level	670 ug/L
Increase fibrinogen level	439mg/dl
Increase LDL level	147 mg/dl

BGA : BGA pH 7.432 pCO2 29.4 mmHg PO2 145.5 mmHg FIO2 80.0 % HCO3- 22 mmol/L SO2c 99.0 % A-aDO2 395.6 mmHg PFR 178.125 (ARDS).

Positive PCR swab, cardiomegaly (LV) chest X-ray and pneumonia brixia score 7, CT scan of the plain head of

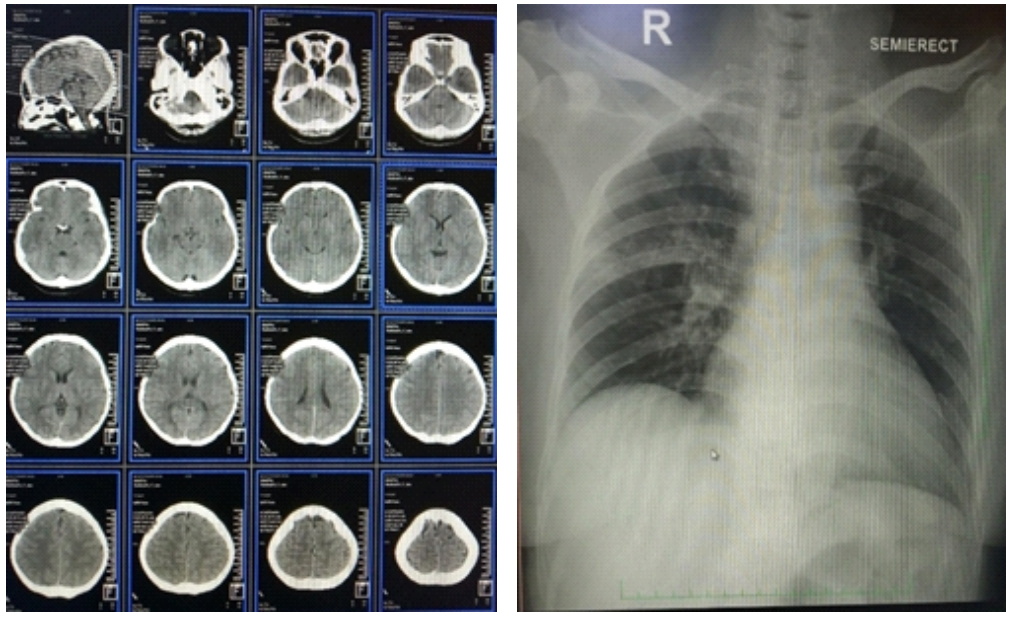

Image 1. Head CT Scan results and Ro Thorax Case 1

lacunar infarction on the posterior crus of the right internal capsule.

The patient was diagnosed with infarction stroke, confirmed covid 19 with ARDS and coagulopathy, dyslipidemia. Treated in the isolation ward with inf levofloxacin 750 mg/24 hours, inj lovenox 0.4cc/24 hours, inj omeprazole 40 mg/12 hours, inj vit B12 drip 1 ampoule/12 hours, inj vit c 1gr/12 hours, aspilet 80 mg/24 hrs, avigan 1600 mg/24 hrs (H1) then 600 mg/12 hrs (H2-H7), atorvastatin 20 mg/24 hrs, colchicine 0.5 mg/8 hrs, n-acetylcysteine 200 mg/8 hrs, paracetamol 500 mg/8 hours, cholecalciferol 1000iu/24 hours, vit B1B6 1 tab/8 hours, zinc 20 mg/12 hours.

After the fifth day of treatment the patient experienced a decrease in condition, appeared short of breath with a respiratory rate of 28x/minute, saturation 90% O2 NRM 10 lpm, BGA pH 7.439 pCO2 32.8 mmHg PO2 65.1 mmHg FIO2 80.0 % HCO3- 27.4 mmol/L SO2c 94.0 % A-aDO2 354 mmHg PFR 81.375 (ARDS), there was an increase in liver function SGOT 231 U/L SGPT 132 U/L without finding markers of viral hepatitis and increased bilirubin. So Avigan was replaced by Aluvia 2 tab/12 hours and treatment in the ICU isolation room.

Treatment in the ICU isolation of the patient has received ventilator support, treatment of COVID 19 infection with TPK 2 times and alluvia 2 tabs/12 hours, bacterial infection with inj meropenem 1gr/8 hours and inj amikacin 1 gr/24 hours, increasing the dose of lovenox 0.6 cc/12 hours, but the condition continued to worsen with inflammatory markers leukocytes 14,400/Ul, CRP 1.57 mg/dl, Ferritin 294.9 ng/ml, Quantitative D-Dimer 5610 ug/L, Fibrinogen 434 mg/dl, Ro thoracic pneumonia brixia score 12. On the 14th day of treatment the patient was declared dead.

Case 2

A 63-year-old man came with complaints of fever for 4 days. 2 days SMRS left limb weakness suddenly only able to fight light resistance, slurred speech, lips drooping to the right, and fever. History of previous illnesses such as previous stroke, hypertension, heart disease, high cholesterol was denied. History of diabetes mellitus controlled with glucodex 80 mg/24 hours. Previously denied contact history with COVID-19 sufferers, the patient had not received the COVID-19 vaccination.

Physical examination obtained GCS E4M6V5, blood pressure 170/80 mmHg, pulse 90x/minute, respiratory rate 20x/minute, temperature 37.5°C, SpO2 98%. Neurologic status: central left VII and XII cranial nerve paresis, left spastic hemiparesis (strength 555/444 555/444). Investigation results showed leukocytosis 13,400/Ul, increased CRP 6.59 mg/dl, increased ferritin 517.5 ng/ml, increased D Dimer 1010 ug/L, increased fibrinogen 534 mg/dl, GDP 158 mg/dl, HbA1c 12.9%, triglycerides 155 mg/dl, LDL 116 mg/dl.

Leukositosis	13.400/Ul
Increase CRP level	6.59 mg/dl
Increase feritin level	517.5 ng/ml
Increase D Dimer level	1010 ug/L
Increase fibrinogen level	534 mg/dl
Increase LDL level	116 mg/dl
Increase GDP level	158 mg/dl
Increase HbA1c level	12.9%,
Increase trigliserid	155 mg/dl,

Positive PCR swab, chest x-ray cor not enlarged, pneumonia brixia score 8, CT scan of plain head lacunar infarction in centrum semiovale and right corona radiata.

The patient was diagnosed with stroke, infarction, confirmed Covid 19 with coagulopathy, diabetes

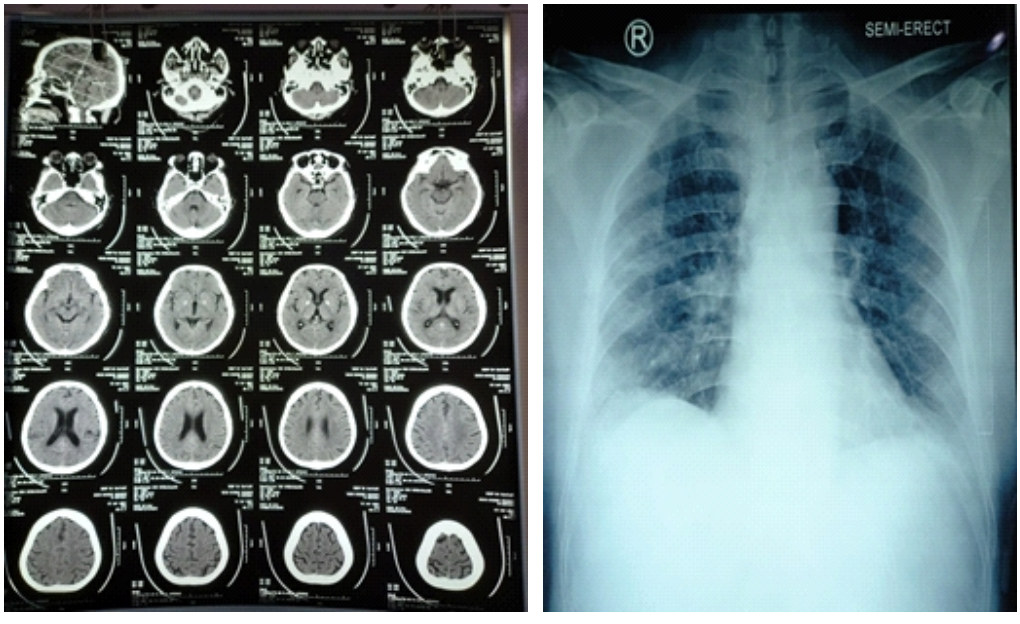

Image 2. Head CT Scan results and Ro Thorax Case 2

mellitus, hypertension and dyslipidemia. The management of this patient was treatment in the isolation ward by administering inj remdesivir 200 mg/24 hours (H1) followed by 100 mg/24 hours (D2-5), TPK 2 times, SP Heparin 750 IU/hour, then 18 IU (pk 22.00), Apidra 6-6-6 IU ac, inj ranitidine 50mg/12 hours, inj vit B12 1 ampoule/12 hours, inj vit C 500mg/12 hours, cilostazol SR 100mg/24 hours, amlodipine 10mg/24 hours, colchicine 0.5 mg/8 hours, n-acetylcysteine 200 mg/8 hours, paracetamol 500 mg/8 hours, cholecalciferol 1000iu/24 hours, zinc 20 mg/12 hours, and physiotherapy.

After 7 days of treatment the patient experienced clinical improvement and decreased inflammatory markers leukocytes 6300/UI, CRP 1.77 mg/dl, ferritin 511 ng/ml, D Dimer 770 ug/L, fibrinogen 439 mg/dl, PCR swab was still positive. Patients continued therapy at home with independent isolation.

DISCUSSION

Covid 19 infection is exacerbated by several co-morbidities such as old age, diabetes mellitus, hypertension, dyslipidemia increasing the risk of stroke infarction in the first and second cases. Endothelial dysfunction is a marker of atherosclerosis associated with vascular risk factors in the form of aging, hypercholesterolemia, hypertension, and hyperglycemia.[8] Endothelial cells are one of the main targets of SARS-CoV-2, patients with pre-existing endothelial dysfunction will be more susceptible to endotheliopathy and disease. vascular.[9]

A hypercoagulable state that causes an increase in pro-inflammatory and pro-coagulant factors, disruption of the endogenous fibrinolytic system, and platelet hyperactivity is also associated with stroke risk factors such as old age, hypertension, and diabetes. Small vessel disease due to hypertension, diabetes, and hyperlipidemia can interfere with the BBB. In addition, comorbidities such as diabetes, hypertension, and hyperlipidemia are risk factors for hypomagnesemia which ultimately increase the risk of cardiovascular disease and stroke.[6,10,11]

The incidence of lacunar infarction in this case is thought to be due to several factors, namely thrombus in the microvascular due to the formation of neutrophil extracellular traps (NETs), activation of complement which causes thrombogenesis and vasculopathy, the formation of antiphospholipid antibodies so that protein c decreases, the formation of microparticles causes platelet hyperactivation and increases tissue factor (TF). resulting in hypercoagulation.[6] The incidence of infarction stroke in cases located in the cerebral area supplied by the middle cerebral artery is in accordance with previous studies which stated that the most common occurrence of infarct stroke due to COVID 19 was in that area.[12] Different from previous studies, most infarct stroke cases were found in blood vessels big.[7,12]

In the first case, advanced stages of COVID have occurred marked by clinically decreased consciousness, ARDS with low saturation, increased inflammatory markers to the occurrence of impaired liver function. At this stage, there has been a cytokine storm that has damaged the blood brain barrier, damaged the endothelium of the blood vessels of the brain, cytokines and SARSCoV-2 have entered the brain parenchyma, thus inducing the death of neurons and the extent of the infarct area in the brain. If the injury has affected the brain stem, it will affect consciousness, breathing and heart work.[13]

The worsening clinical condition in the first case was also suspected to be due to the inflammatory factor of the COVID 19 virus which could not be controlled as seen from the high inflammatory markers despite treatment, the occurrence of ARDS and impaired liver function. This is in accordance with previous studies which stated that the mortality rate of stroke cases in COVID-19 patients was higher, especially in patients with diabetes, atrial fibrillation, impaired liver function, and congestive heart failure.[14] The treatment given was according to standards, using a mechanical ventilator, antiplatelet, anticoagulant, antiviral and anti-inflammatory. At this stage, it is necessary to consider giving double antiplatelet or TPA.[13]

The second case had middle stages of COVID with neurological deficits and increased inflammatory markers in the patient. At this stage there has been an uncontrolled cytokine storm, endothelial inflammation, platelet activation, NET formation, microparticle release, complement activation, with a hypercoagulable state that increases the risk of stroke.[13] Controlled viral inflammatory factors and good comorbid control lead to clinical improvement and reduction of inflammatory markers in these patients. The management given is in accordance with the standards, including anticoagulants, antivirals, anti-inflammatories, statins.

CONCLUSION

There were 2 cases of stroke infarction in patients with COVID 19 who had comorbidities. The first case with advanced stages of COVID experienced a worsening of the condition despite being given appropriate therapy. The second case with middle stages of COVID experienced an improvement after the viral inflammatory factors were controlled and comorbid was well controlled. The incidence of stroke in patients can be caused by various causes, one of which is COVID-19 infection.

CONFLICT OF INTEREST

In this case series there is no conflict of interest.

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AUTHOR GUIDELINE

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Research manuscript should adhere guidelines as follow:

Title :
1. Is neither too long nor too short, approximately 12–14 words
2. Describes research design
3. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, method, result, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (research justification): what have been known and what need to be added. The second paragraph consists of hypothesis or research aim.
2. Is supported by relevant and strong references

Methods :
1. Explains research design, settings and time
2. Explains population and sample, sampling technique, sample size (equation doesn't need to be enclosed), inclusion and exclusion criteria.
3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
4. Thoroughly explains method, instrument, measurement technique and data collection
5. Explains data analysis with proper tests according to data, significance and confidence interval
6. Explains computer program (software) used
7. Explains ethical clearance and informed consent

Results :
1. Is presented in a logical sequence
2. Presents subject characteristics (in a table). For clinical trial, subject characteristic of each group before trial are presented
3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
5. Provides hypothesis without commentary

Discussion :
1. Discusses all relevant findings and its association with practice. There is no redundant repetition of findings already presented in the results section.
2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
1. Should answer research question
2. Should be based on research findings, not quotation
3. Can provide suggestion for future research

References :
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1. Present complete name of authors without academic title along with office/institution/work place address under the title
2. Provide correspondences
   The main author provides a statement explaining that article has never been published nor sent for publication to other journals and has already been approved by all co-authors evidenced by a statement sheet. All sent articles are reviewed by profession groups (peer reviewers) and editors. All articles should provide ethical clearance issued by Ethical Review Board and 2 sheets of inform consent form already signed in "pdf" format.

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1. Is neither too long nor too short, approximately 12-14 words
2. Contains no abbreviation unless standard

Abstract :
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2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (justification of the case report). The second paragraph consists of aim of case report emphasizing diagnose/pathogenesis/therapy.
2. Is supported by relevant and strong references

Case report :
1. Presents short case involving medical history, physical examinations, and investigations.
2. Stresses new or rare cases or new therapies or procedures
3. Provides patient's picture (if necessary), investigations such as radiology or laboratory or others as needed. Pictures/photos size minimum 300 dpi.
4. Obtains patients' or families' informed consent for publication for patients with easily identified features. Editors may conceal physical features considered unnecessary.
5. Contains maximum four photos/pictures for each article.

Discussion :
1. Provides epidemiology data showing that rare cases occur or new procedures are conducted.
2. Provides relevant discussion according to aim of the case report emphasizing diagnose/pathogenesis/therapy comparing/relating to other cases and providing LoE (Level of Evidence).

Conclusion and suggestion :
1. Are in line with the aim of case report.
2. Suggestion consists of improvement for case management.

Reference :
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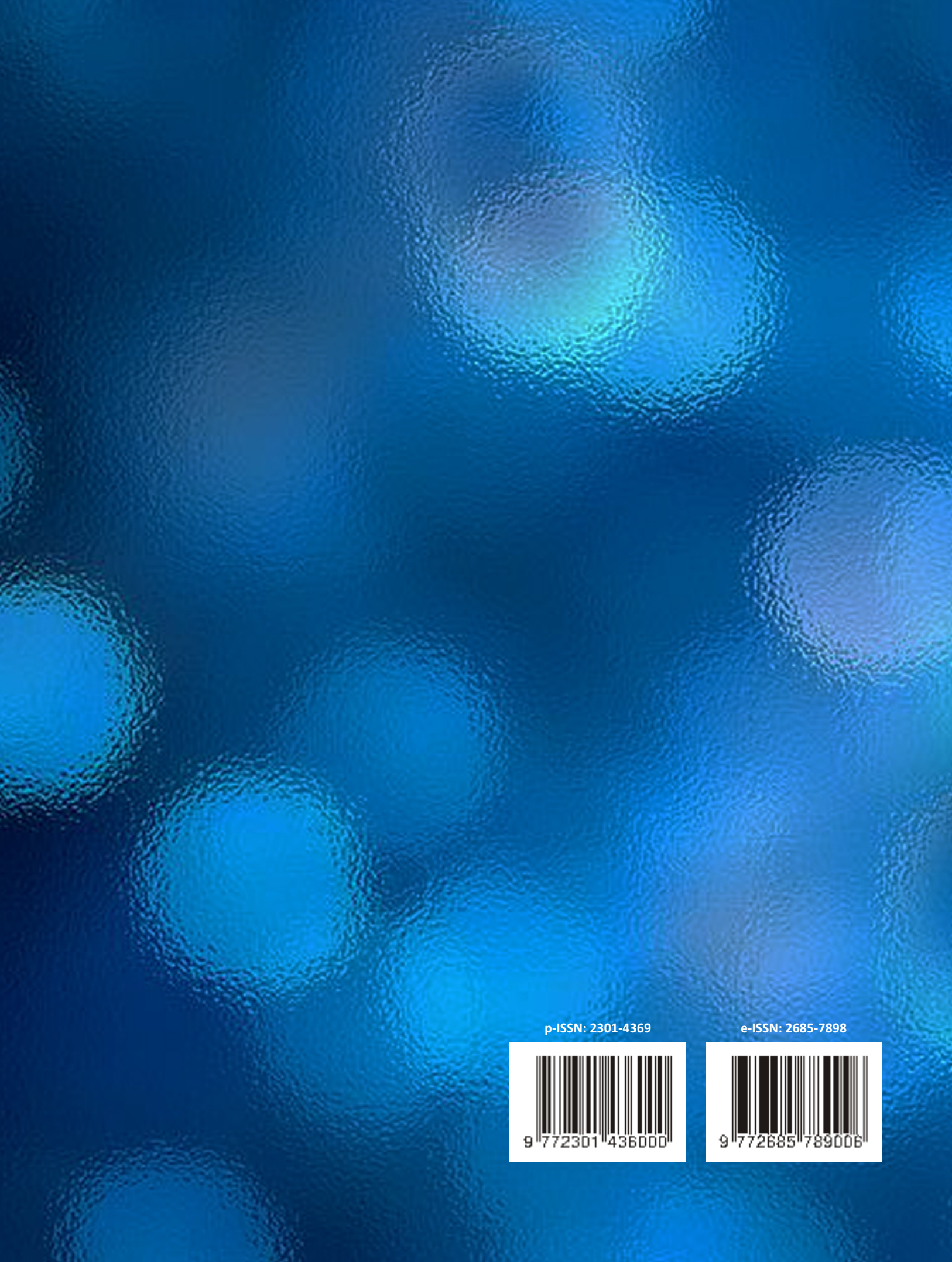

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