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Accuracy of Kampala Trauma Score as a Predictor in Assessing the Prognostic Value of Multiple Trauma

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Abstract

Determining a trauma scoring system appropriate for certain conditions will help in predicting mortality and morbidity, and can determine the need for treatment in patients. Kampala Trauma Score (KTS) is a trauma scoring system that uses a decent number of assessment variables and can be used in all general groups. This study was a retrospective prognostic test conducted in Dr. Hasan Sadikin Hospital Bandung, Indonesia, from December 2021 to July 2022. Data obtained was processed using Microsoft Excel and SPSS spreadsheets. The respondents were 66 people with multiple trauma. Results showed that this study was dominated by patients with blunt trauma (n=63, 95.45%). The mean KTS score in this study was 13.08±1.03. In 49 (74.24%) patients who survived, the mean KTS score was 13.41±0.89 and in 17 (25.76%) patients who died, the mean KTS score was 12.12±0.79. The greatest mortality accuracy was at the cutoff point of the KTS score >12 (81.82% accuracy; 70.59% sensitivity; 85.71% specificity). The accuracy value of the KTS score is in line with the ROC where the optimal KTS score is >12 (85.77%). In conclusion, the Kampala trauma score can be used as a predictor in assessing the prognostic value of multiple trauma patients with the obtained cut-point value as it has high accuracy, sensitivity, and specificity values.

Keywords: Accuracy, KTS, multiple traumas, trauma scoring

Introduction

Trauma is an important health problem in developing countries.[1] Deaths caused by trauma are still high and even increasing in the world.[2] The most common cause of trauma is traffic accidents.[3] It is estimated that the number of deaths from traffic accidents is one million deaths each year, with 20 to 50 million serious injuries annually. Trauma is the main cause of death in Indonesia in the age group of 15–24 years and the number two in the age group of 25–34 years.[4] According to data from Police Department of Indonesia, in 2015 there were 38,279 cases of road accidents with the most victims in the 15–55-year age group. The trauma that occurs often involves several regions of the body, which is referred to as multiple traumas.[5]

Multiple trauma is an injury to two or more organ systems with a fairly high degree of injury and is accompanied by a systemic reaction to life-threatening trauma.[6] The incidence of trauma is increasing along with the increasing number of motorized vehicle users who do not obey traffic signs and do not comply with the use of complete personal protective equipment.[6] Previous studies explained that there were 126 multiple trauma patients with a mortality of 16.6%.[6] The majority of trauma patients (50–60%) die on the way to the hospital.[3] Previous studies also explained deaths in trauma patients were divided into 3 categories, namely immediate death (45%), early death within 1–4 hours (34%), and late death over 1 week (20%). Each category has a different cause of death, namely trauma to the central nervous system and cardiovascular system in immediate and early death, then late death, mostly due to systemic complications such as sepsis or multiple organ failure.[7] Estimating the severity of trauma is a good strategy, not only for

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estimating mortality but also for determining the need for patient care on admission. Estimating the severity of this trauma, will not only reduce mortality and morbidity but can also reduce complications that can result from the trauma itself.[8]

To estimate the severity of the trauma, many studies have developed a scoring system or trauma assessment. This trauma scoring system has a significant function to predict prognosis and can determine the appropriate treatment.[2] Several scoring systems have been successfully developed in the last few decades. The trauma scoring system is divided into several types, including the anatomical trauma scoring system, such as the Injury Severity Score (ISS). Then the physiological trauma scoring system, such as the Revised Trauma Score (RTS), and the mixed trauma scoring system, namely the Trauma and Injury Severity Score (TRISS) and the Kampala Trauma Score (KTS).[9]

Kampala Trauma Score (KTS) is a trauma scoring system that focuses on assessing the patient's body physiology compared to the patient's anatomy. KTS was created and developed in a developing area, where access to technology is still limited to carry out an accurate evaluation of the patient's anatomical factors.[10] According to a study conducted by Manoochehry et al., This scoring system has a sensitivity of 88% and a specificity of 73%. the positive-likelihood ratio is 8.90, and the negative-likelihood ratio is 0.16.[11] Although the KTS was developed to simplify the way of predicting mortality in low-middle income countries, from the meta-analysis studies conducted, this scoring system has higher accuracy than the RTS scoring system.[11] The KTS scoring system is easy to use without the need for special needs, such as expertise, and injury flashbacks. So that KTS is very possible and can be used as a first line in triage, this scoring system can be used to predict mortality and the need for hospitalization.[11, 12]

Determining a trauma scoring system that is appropriate for certain conditions will help in predicting mortality and morbidity and can determine the need for treatment in patients.[12] Until now, there have been no studies assessing the prognostic ability of the KTS system in Dr. Hasan Sadikin General Hospital Bandung, so no data are showing the sensitivity, specificity, or ability to determine the prognosis of KTS in Dr. Hasan Sadikin General Hospital Bandung. therefore, this study was conducted. This study aims to determine the accuracy of KTS in assessing the prognostic value of multiple trauma patients at Hasan Sadikin Hospital Bandung.

Methods

This study is a prognostic study with a retrospective cohort design to determine the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and mortality calculated from the KTS scoring system. The subject of the study was the medical records of multiple trauma patients who came to Dr. Hasan Sadikin General Hospital Bandung from 2017 to 2021 and who met the inclusion criteria.

The inclusion criteria in this study were the patient suffered from trauma to more than one organ, the wound was serious (reversible wound, but requires hospitalization), severe (life-threatening wound, and will not heal if not given treatment), critical (threatening mental health and not necessarily cured even though medical treatment is given), the patient is >18 years old, and the onset of trauma is less than 24 hours from the occurrence of the trauma. Exclusion criteria in this study were trauma patients who had a history of comorbid disease, patients in a triad of death condition when they arrived, including coagulopathy, hypothermia, and metabolic acidosis, patients who had been resuscitated in a previous health facility, and incomplete medical record data.

The sample size based on the rule of thumb in our study requires at least 60 medical records. The data taken are secondary data from patients with multiple trauma who come to Dr. Hasan Sadikin General Hospital Bandung, namely through medical records. Data taken in the form of age, gender, age, level of consciousness (GCS and AVPU), blood pressure, respiratory rate, and also the number of serious injuries assessed by several even numbered interterraters, at least 2 people. Furthermore, data on the comorbidities that exist in the patient is carried out, to reduce bias in the study. The data obtained was processed by editing, coding, data entry, and cleaning stages using Microsoft Excel spreadsheets and SPSS for Windows with a value < 0.05 showing a significant result.

The research was conducted at Dr. Hasan Sadikin General Hospital Bandung from December 2021 to July 2022. The research has received ethical clearance number: LB.02.01/X.6.5/46/2022 from the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung.

Results

The number of samples in this study was 66 patients who met the inclusion criteria. The sample consisted of 58 men (87.88%) and 8 women (12.12%). The average age in the study sample was 33.32±17.40 with the youngest age being 16 years old and the oldest being 93 years old. The largest age group is in the range of 16-25 years. The type of trauma was dominated by blunt trauma as many as 63 patients or 95.45%. The mean KTS score in this study was 13.08±1.03.

The number of samples with living outcomes of as many as 49 (74.24%) and dead outcomes of as many as 17 samples (25.76%). The male sex group consisted of 43 living outcomes (65.14%) and 15 dead outcomes (22.73%) while 6 samples (9.09%) were alive and 2 samples (3.03%) died. The living group had a mean age of 32.65±18.22 years and the dead group had a higher mean age of 35.24± 5.14 years. Out of life with blunt trauma as many as 46 samples (69.70%) and sharp trauma by 3 samples (4.55%) while the outcome of death all had blunt trauma type as many as 17 samples (100.00%). The KTS score on the live outcome had an average of 13.41±0.89 while the dead outcome had a KTS mean of 12.12±0.78.

The KTS score had a significant relationship with patient outcomes with $p < 0.001$ with a mean value of 13.41±0.89 on survival and 12.12±0.78 of death. The variable that has a significant relationship with patient outcomes is GCS/AVPU with $p<0.001$. The GCS score on the live outcome had a mean of 12.94±2.45 and that of the dead outcome had an average of 6.35±2.09. The AVPU variable had a mean outcome of 3.57±0.71 for living patients and 1.94±0.24 for dead patients. Other variables, namely age, systolic blood pressure, and respiratory rate were not significantly related to the patient's outcome in this study with p-values of 0.570, 0.851 and 0.249, respectively.

In the age variable, the sample with a live outcome had a mean age of 32.65±18.22, while the sample with a dead outcome had a mean age of 35.24±15.14. Systolic blood pressure in living patients had a mean of 112.24±22.104 while the mean of dead patients was 111.18±9.33. The respiratory rate in the living patients had a mean of 22.29±3.70 and in the dead patients it was 23.41±3.30.

The greatest accuracy is at the cut-off point of the KTS score > 12 with an accuracy of 81.82%, sensitivity 70.59%, specificity 85.71%, PPV 63.16%, NPV 89.63%, LR+ 4.94, and LR- of 0.34.

The greatest accuracy value is also in line with the ROC as shown in Figure 1, namely the most optimal cut-off point is in the KTS score > 12 with an AUC value of 85.77% which shows the KTS score has a high accuracy prediction on the mortality of multiple trauma patients.

The optimal cutoff value can be seen based on Figure 2, which is found that the cutoff value between sensitivity and specificity is at COV 12 and 13. respectively, by 100% and 55.10% so the optimal cut-off point for KTS is 12, which means that patients with KTS >12 have a good prognosis and KTS 12 have a poor prognosis.

On table 5 in the 2x2 chi-square calculation with COV KTS 13, the P value is <0.0001. This shows that there is a correlation between patient outcomes and the cutoff value of KTS 13.

Table 1 KTS Scoring

Description	Score
Age (in years)	
5–55	2
<5 or >55	1
Systolic blood pressure on admission (mmHg)	
>89	4
50–89	3
1–49	2
Undetectable	1
Respiratory rate (breath per minute)	
10–29	3
≥ 30	2
≤9	1
Neurological status (AVPU system)	
Alert	4
respond to Verbal	3
respond to Pain	2
Unresponsive	1
Number of serious injuries	
None	3
1	2
≥2	1

Table 2 Characteristics of Research Patients

Characteristics	Life	%	Death	%	Total	%
Gander						
Male	43	65.15	15	22.73	58	87.88
Female	6	9.09	2	3.03	8	12.12
Age (years)*	32.65 ± 18.22		35.24 ± 15.14		33.32 ± 17.40	
16–25	26	39.39	7	10.61	33	50.00
26–35	7	10.61	2	3.03	9	13.64
36–45	5	7.58	4	6.06	9	13.64
46–55	4	6.06	2	3.03	6	9.09
56–65	4	6.06	1	1.52	5	7.58
>65	3	4.55	1	1.52	4	6.06
Type of Trauma						
Blunt	46	69.70	17	25.76	63	95.45
Sharp	3	4.55	0	0.00	3	4.55
KTS Score*	13.41 ± 0.89		12.12 ± 0,78		13.08 ± 1.03	
Patient outcome						
Life					49	74.24
Death					17	25.76

*Average ± Standard Deviation

Discussion

All samples were grouped based on their prognoses, namely alive and dead to be tested for sensitivity, specificity, NPV, PPV, LR+, LR-, and cut-off value (COV) of KTS scores as predictors of the prognosis of multiple trauma patients. The KTS score was chosen because the trauma scoring system focuses on assessing the patient's body physiology compared to the patient's anatomy. KTS was created and developed in a developing area, with limited access to technology to carry out an accurate evaluation of the patient's anatomical factors.[2] KTS was developed to simplify the way of predicting mortality in low-middle income countries, but from the meta-analysis studies conducted, this scoring system has higher accuracy than the RTS scoring system, because KTS has a significantly higher sensitivity than RTS. The RTS also has a>

Table 3 The Relationship of the Composing Variables of KTS with Patient Outcomes

Variable	Life	Death	P value*
Age			
Average ± SD	32.65 ± 18.22	35.24 ± 15.14	0.570
Systolic BP			
Average ± SD	112.24 ± 22.104	111.18 ± 19.33	0.851
GCS			
Average ± SD	12.94 ± 2.45	6.35 ± 2.09	0.001
AVPU			
Average ± SD	3.57 ± 0.71	1.94 ± 0.24	0.001
RR			
Average ± SD	22.29 ± 3.70	23.41 ± 3.30	0.249
KTS			
Average ± SD	13.41 ± 0.89	12.12 ± 0.78	0.001

*T-test

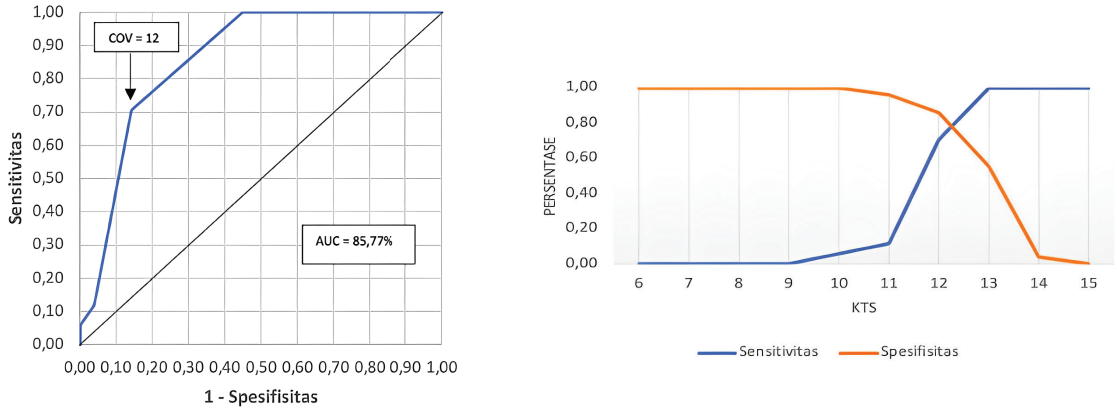

Figure 1 (a) ROC KT Score with Multiple Trauma Patient Outcomes (b) Optimal Cut-Off Point of KTS on Sensitivity and Specificity Of Outcome In Multiple Trauma Patients

Table 4 KTS scoring system diagnostic accuracy

KTS (Score)	Accuracy	Sensitivity	Specificity	PPV	NPV	LR+	LR-
>6	74.24%	0.00%	100.00%	-	74.24%	-	1.00
>7	74.24%	0.00%	100.00%	-	74.24%	-	1.00
>8	74.24%	0.00%	100.00%	-	74.24%	-	1.00
>9	74.24%	0.00%	100.00%	-	74.24%	-	1.00
>10	75.76%	5.88%	100.00%	100.00%	75.38%	-	0.94
>11	74.24%	11.76%	95.92%	50.00%	75.81%	2.88	0.92
>12	81.82%	70.59%	85.71%	63.16%	89.63%	4.94	0.34
>13	66.67%	100.00%	55.10%	43.59%	100.00%	2.23	0.00
>14	28.79%	100.00%	4.08%	26.56%	100.00%	1.04	0.00
>15	25.76%	100.00%	0.00%	25.76%	-	1.00	-

KTS: Kampala Trauma Score; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR: Likelihood Ratio

45-degree diversion from the calibration line on the comparison chart for trauma severity measurements.[9] This KTS scoring system is easy to use without requiring special needs, such as experts, injury flashbacks, so that KTS is very possible and can be used as a first line in triage, besides this scoring system can be used to predict mortality and the need for hospitalization.[9, 10]

A scoring system to predict mortality that is easy to do is needed because multiple trauma has a high mortality rate.[6] The multiple trauma mortality rate found in this study was 25.8% higher than that reported by the previous study by 16.6%. In the same previous study, there were more patients with multiple trauma who met the inclusion criteria than in this study, 126 patients

Table 5 Relationship between COV 12 KTS and Patient Outcome

Variable	Output		P value*
	Death	Alive	
KTS ≤ 12	12 (0.18%)	7 (0.11%)	
KTS > 12	5 (0.07 %)	42 (0.64%)	<0.0001
Total	17	49	

*Chi-Square Test

and 66 patients, respectively.[6]

The KTS score ranges from 5-16, with the most reported score being a perfect score of 16. In other words, the patient has normal physiological parameters, ages 5–50, and there are no serious injuries. KTS scores have a distribution that is generally skewed to the left (dominated by data that is closer to physiological normal than close to trauma classification) as in previous studies.[1] This also happened in the results of this study, the KTS score was distributed to the left with the highest score being at KTS 14 and followed by KTS 13 and 12.

In conducting the KTS score validation test, we first tested the sensitivity and specificity of the COV KTS scores ranging from 6 to 15. Then, this study also analyzed the sensitivity and specificity values in this study with those of previous studies. Based on research from Macleod et al. obtained COV 13 with sensitivity and specificity of 92.1% and 47.3% respectively, while in this study with COV 13 the sensitivity and specificity were 100% and 55.1%, respectively.[1] Then based on research from Oluwadiya et al. The optimal COV in this study was 12 with a sensitivity of 100% and a specificity of 70.7%, while with a COV of 12 in this study, a sensitivity of 70.59% and a specificity of 85.71% were obtained.[13] Previous study also obtained the most optimal COV value is 12 with a sensitivity of 90% and specificity of 88%.[10] In another previous study also obtained a sensitivity of 66.07% and a specificity of 77.55%.[14]

Then, we determine the most optimal COV in this study using the ROC curve. Analysis of the ROC curve shows that the optimal COV in this population is a KTS score > 12 and has an AUC of 85.77% with a sensitivity and specificity of 70.59% and 85.71%, respectively, and has an accuracy of 81.82%. When compared to the meta-analysis conducted by Manoochehry et al.[11] which has a sensitivity of 88% and a specificity of 73%, the sensitivity value in this study is lower and the specificity value is higher.The LR+ value in this study was strengthened compared to the meta-analysis from 3.30 to 4.94 even though both had a small increase in the output, while the LR- value was attenuated from 0.16 which was a moderate increase to 0.34 which is a small increase. The odds ratio (OR) obtained in this study shows that the group of patients with KTS > 12 will have a mortality rate of 14.4 times greater than that of patients with KTS 12. The odds ratio is smaller than the meta-analysis conducted by Manoochehry et al. with an OR value of 20.[11] The PPV value in this study with COV 12 was obtained at 63.16% so that it showed the ability of KTS in predicting the outcome of death when KTS >12 was 63.16% while the NPV value was obtained at 89.63% so that it showed the ability of KTS in predicting the outcome of life when KTS 12 of 89.63%. These results indicate that COV 12 has high accuracy, sensitivity, specificity, PPV, NPV, LR+, and LR- so it can be used as a predictor of prognosis for multiple trauma patients.

The advantage of this research is that it is carried out at the referral hospital of West Java Province so that it can describe the population in West Java and in the future the results of this study can also be used clinically West Java Province, especially in type C network hospitals because the Kampala trauma score is simple and easy to apply. However, this study has limitations, namely that the sample is not large enough to provide a possible mortality percentage that cannot describe the level of mortality in the population. The severity of the patients included in the study also did not vary as indicated by the sample that was only in the KTS range of 10 to 15 while the KTS with scores <10 and 16 had 0 samples which certainly affected the sensitivity, specificity, and accuracy of the research results.

The Kampala trauma score can be used as a predictor in assessing the prognostic value of multiple trauma patients with the cut-point value that has been obtained because it has high accuracy, sensitivity, specificity, PPV, NPV, and LR values. The KTS value with a cut-off point of 12 can be used as a reference for predicting patient mortality. Clinicians can use the Kampala trauma score in determining the prognosis of multiple trauma patients in areas with inadequate equipment. There is a need for further research with a larger number of samples and a more diverse population and a more proportional number of outcome samples, and the need for an assessment of critical and fatal injuries to Kampala's scoring.

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Continuous Ambulatory Peritoneal Dialysis Cost-Effectiveness in National Health Insurance Era of Indonesia

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Abstract

Essential treatments for patients with end-stage renal disease include Renal Replacement Therapy (RRT) consisting of hemodialysis, peritoneal dialysis, and kidney transplantation. In 2014, dialysis coverage in Indonesia was more than 1.5 trillion, making it the second highest expense in the National Health Insurance (BPJS) expenses. This study compared the cost-effectiveness between Continuous Ambulatory Peritoneal Dialysis (CAPD) and Hemodialysis (HD) in patients treated in Dr. Hasan Sadikin General Hospital. Data were collected from the Urology Department from 2014 to 2017. This was a retrospective observational study on 3 groups of patients: patients with effective CAPD each year as the first group; patients who had experienced repair of CAPD and continued to use it as the second group; and patients who discontinued CAPD due to complications and returned to hemodialysis as the third group. Each group expense was calculated with standard cost insurance for one year in the hospital. The expense was then be compared to the expense of hemodialysis for one year. A total of 89 patients in the CAPD program from 2014–2017 were treated at the department. When compared to HD, the first, second, and third group of CAPD patients experienced a cost reduction of IDR 23.227.857/person, IDR 18.127.857/person, and IDR 1.661.972.000, respectively. Total savings from the CAPD program in the hospital was IDR 1.661.972.000 from 2014. It is then concluded that CAPD could reduce the burden of government insurance in a cost-effective manner and is considered a treatment of choice in the National Health Insurance Era.

Keywords: Chronic kidney disease, continuous ambulatory peritoneal dialysis, cost-effectiveness analysis, hemodialysis national health insurance

Introduction

Chronic kidney disease (CKD) has become a challenging issue worldwide, with an estimated prevalence of 13.4% (11.7–15.1%). Globally, approximately 4.902 and 7.083 million patients with end-stage renal disease (ESRD) are expected to require renal replacement therapy. Considering the rising rate of non-communicable diseases and the population continues to age, the concern of ESRD also keeps growing. [1]

The prevalence of CKD in Indonesia has been drastically increasing to nearly 0.2% of the total population. Of these number, the risk of developing ESRD is found in about 482,000. Approximately 18,163 individuals have ESRD in Indonesia.[2] Important treatments for patients with ESRD include renal replacement therapy, which consists of hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. Although kidney transplantation is still considered the most effective treatment for ESRD, the options of treatment are only limited to hemodialysis or peritoneal dialysis due to the rarity of living organ donors and cadaveric donors that are poorly accepted. In addition, kidney transplantation is not feasible considering the increasing incidence and prevalence of ESRD (35,000 and 120,000, respectively). Furthermore, Indonesia Renal Registry stated that around 80% of patients with ESRD are treated with hemodialysis as the most suitable choice, with peritoneal dialysis at only 2%.[5]

The Health Social Security Institution (BPJS) initially launched a national health insurance scheme that is premium-based in 2014. The scheme's objective was universal health coverage for approximately 250 million populations

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by 2019. This insurance scheme reimbursed all dialysis treatments, with a higher rate for hemodialysis compared to peritoneal dialysis. There are approximately only 53% of patients with dialysis access, and nearly all patients are undergoing hemodialysis.[2] In 2014, over IDR 1.5 trillion was spent on dialysis coverage, making it the second highest expense for BPJS.[6] Several economic evaluations have been conducted to evaluate the impact of dialysis financially due to this high-cost burden on the healthcare system worldwide.[7-11]

This research was conducted to determine the cost-effectiveness between Continuous Ambulatory Peritoneal Dialysis (CAPD) and Hemodialysis (HD) in Hasan Sadikin General Hospital.

Methods

Data was collected from the Urology Department from 2014 to 2017. The method of study was retrospective observational. Subjects were ESRD patients who underwent CAPD insertion. The subjects were divided into 3 groups; the first group was patients with effective CAPD each year, the second group was patients who had experienced repair of CAPD and continued to use it, and the third group was patients who discontinued CAPD due to complications and returned to hemodialysis. Each group expense would be calculated with standard cost insurance for one year in Dr. Hasan Sadikin General Hospital Bandung. The CAPD expense would be compared to hemodialysis expense for one year using incremental cost-effectiveness measure. The ethical clearance for this research was obtained from the Research Ethical Committee of Dr. Hasan Sadikin General Hospital Bandung.

Result

From 2014 to 2017, Urology Department had

Table 1 Assurance Coverage Price

Item	Assurance Coverage (Rupiah)
CAPD operation	5.100.000
Dianeal/day	221.000
Hemodialysis	1.025.000
Arteriovenous shunt	2.100.000

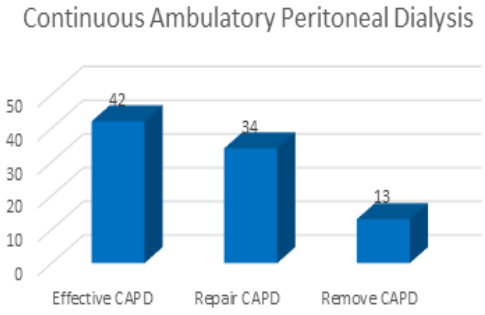

Figure 1 Total CAPD patients from 2014-2017

89 patients in the CAPD program. There were 56 males and 33 females with a mean age of 30 years old. All patients were divided into 3 groups, effective CAPD group 42 (47%) patients, repair group 34 (38%) patients, and removal CAPD group 13 (14 %) patients. The mean effective duration for peritoneal dialysis in 1 year was 365 days for the effective group, 37 days for the repair group, and 45 days for the last group.

The mean cost for the first group was IDR 85.765.000/year/person, IDR 90.865.000/year/person for the second group, and IDR 103.604.011/year/person for the third group. As the cost for each hemodialysis patient was about IDR 108.992.857 for a year, every CAPD group had a lower burden than HD.

The most considerable saving came from the first group with IDR 975.570.000 with a mean benefit of IDR 23.227.857 for each patient. Saving from the second CAPD group was IDR 616.347.143 with a mean benefit of IDR 18.127.857 for each patient. The patient who removed CAPD and continued hemodialysis had the least saving with IDR 70.055.000 and a mean benefit of IDR 5.388.846 for each patient.

Total savings from the CAPD program over

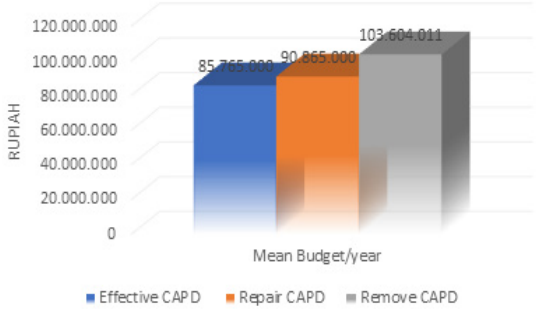

Figure 2 Mean Peritoneal Dialysis Budget A Year for Each Group

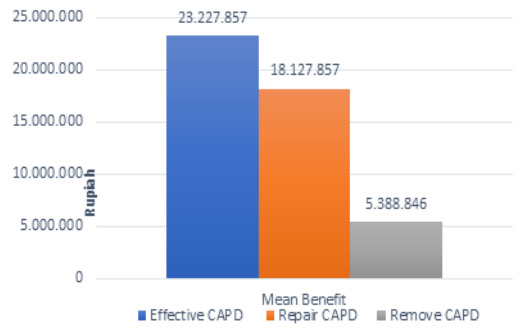

Figure 3 Saving Budget For Each Person with PD Over HD in A Year

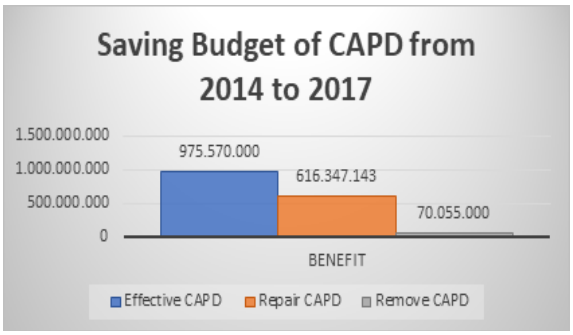

Figure 4 Saving Budget of CAPD from 2014 to 2017

HD was IDR 1.661.972.000 from 2014-2017 in Dr. Hasan Sadikin General Hospital Bandung.

Discussion

Dialysis is performed in two forms: hemodialysis (HD) and peritoneal (PD). The mechanism of hemodialysis is filtering blood to remove toxic, excessive fluid and salts using a machine. Hemodialysis was firstly used in 1967 in Indonesia and has continued to be used to handle ESRD patients. There were approximately 382 operating centers across the country in 2015.[3] Another dialysis method is peritoneal dialysis (PD), which uses the peritoneal membrane as a dialysis solution. The most commonly used in Indonesia is continuous ambulatory peritoneal dialysis (CAPD); however, the solution has to be changed up to 4 times/day.[12] The National Health Insurance of Indonesia (JKN) covers two-times/week HD sessions with various reimbursements that depend on the classes, ranging from IDR 786,200 to IDR 982,400.[13] Literature have shown that peritoneal dialysis has higher cost-effectiveness; however, it is still underperformed. This issue occurs because many dialysis centres in Indonesia are still unwilling to conduct PD, with only 3% of PD out of 30,544 patients undergoing dialysis.[4] Other countries have shown a much higher proportion of PD out of the total dialysis. A study in Hong Kong showed a ratio of nearly 3:1 for PD compared to hemodialysis (71.8% to 25.6%).[14] The reason for such a higher proportion is that peritoneal dialysis is more cost-effective compared to hemodialysis in developed countries. The differences between hemodialysis and peritoneal dialysis from a cost-effectiveness perspective are the healthcare employees' incentives and logistic resources. Hemodialysis costs more than peritoneal dialysis regardless of the addition of adjustment.[11,15] However, some developing countries have a higher unit cost (contributed by the delivery cost of dialysis soluble used in PD) of peritoneal dialysis compared to hemodialysis.[2] Furthermore, the primary reason for a low rate of PD in Indonesia is limited knowledge and the reluctance to promote peritoneal dialysis. Peritoneal dialysis is difficult to implement because of insufficient data regarding costs and quality of life, and healthcare professionals. Furthermore, since Indonesia is geographically vast, access and transportation are very limited, leading to limited dialysis access in remote areas.[2] In order to convince decision-makers and stakeholders to expand peritoneal dialysis for patients in remote areas, in which weekly HD routine seems impossible, studies regarding the quality of life and costs of patients with ESRD are necessary. The primary research question is how cost-effective PD differs from HD.[2]

The results of these studies indicated that PD had more saving for the JKN burden. Even the patient who had ineffective CAPD and went back to hemodialysis still provided some cost-benefit to the government insurance system. Total saving from the CAPD program over HD was IDR 1.661.972.000 from 2014-2017 in Dr. Hasan Sadikin General Hospital Bandung. The optimal PD should be considered with the best surgical technique and a skilful surgeon to reduce the incidence of ineffective CAPD. This is means that surgeon who want to insert CAPD catheter must have licences/qualified for this.

CAPD is concluded to reduce the burden of government insurance cost-effectively. The optimal PD should be considered a superior treatment choice to HD in National Health Insurance Era.

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Correlation Between Physical Activity and Fitness Level Among Anesthesiology and Intensive Care Residents

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Abstract

Anesthesiologists have a highly varied scope of work. Previous studies demonstrated that the physical activity of anesthesiologists and their residency program in the work environment does not meet the recommended standards. This study aimed to determine the relationship between physical activity and level of physical fitness among anesthesiology residents. This study was an analytical observational study with a cross-sectional design conducted on residents of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Padjadjaran, Indonesia, between January and April 2022. All anesthesiology residents were asked to fill out the International Physical Activity Questionnaire (IPAQ) and had their number of steps measured using a pedometer while the physical fitness level was assessed using the Harvard Step Test. Physical activity was assessed based on the IPAQ and pedometer. The results of IPAQ measurement showed that more subjects had low physical activity (n=44) compared to good physical activity (n=31). When measured using a pedometer, 38 subjects were classified as having low physical activity while 36 had good physical activity. Low fitness level (n=43) was associated with less physical activity on IPAQ (41 and 2) and pedometer (30 and 13). No residents had moderate or better fitness levels. Correlation analysis between physical activity and physical fitness showed a significant positive correlation with a p-value <0.05 (Spearman Rho: 0.618). Thus, physical activity and fitness level are well-correlated among of Anesthesiology and Intensive Care residents.

Keywords: Anesthesiologist resident, fitness level, physical activity

Introduction

Anesthesiology and Intensive Therapy is a medical specialty that has a varied scope of tasks involving the operating room, resuscitation room, intensive care room, and treatment room.[1] Previous study conducted in Department of Anesthesiology, Perioperative and Pain Medicine at the Brigham and Women's Hospital showed that Anesthesiology and Intensive Care residents does not meet the standards recommendations developed by WHO.[2] Anesthesiologists are reported to be less active than other specialists.[3] High working hours in training limit the ability of residents to engage in regular physical activity, leading to increased health risks.[4] Physical activity is an important determinant and predictor of fitness level.[5, 6]

Low fitness level is associated with decreased learning abilities, decreased performance, and long-term effects in the form of a decrease in service quality, resulting in medical errors that may endanger patients.[7] Proper physical activity can improve fitness related to physical ability in a static, dynamic, and motoric manner.[8, 9] Several factors that may affect the assessment of fitness levels include age, gender, genetics, diet, and a healthy lifestyle.

Despite there are well-documented study regarding physical activity and physical fitness among Anesthesiology and Intensive Care residents worldwide, there had been no research conducted in Indonesia. The study aims to reveal correlation and determine the association between physical activity and fitness levels of Anesthesiology and Intensive Care residents in Dr Hasan Sadikin General Hospital, Bandung.

Methods

This study is an analytic observational study

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with a cross-sectional design. The subjects of this study were the residents of Anesthesiology and Intensive Therapy in Hasan Sadikin General Hospital Bandung. The study was conducted in the lecture room in Department of Anesthesiology and Intensive Care Dr. Hasan Sadikin General Hospital Bandung from Januari to April 2022 after obtaining approval from the Health Research Ethics Committee Dr. Hasan Sadikin General Hospital with Number LB.02.01/X.6.5/350/2021.

The minimum sample formulated by modified Cochran formula for observational studies through unpaired categorical analysis approach with α <0.05 and power 0.95 was 60 residents who are actively working in the anesthesia service of Dr. Hasan Sadikin General Hospital Bandung and signed the informed consent to participate in this study were included in this study. Study subjects did not take the duty shift on one day before the fitness level measurement, if so the examination will be rescheduled. The exclusion criteria of this study are residents who are pregnant; have BMI over 30 kg/m^2; and are known to have cardiac or lung disease previously diagnosed by cardiologist or pulmonologist, through history taking and physical examination. Data collected included age, sex, and body mass index. Measurement of physical activity in this study used subjective and objective examinations. Physical activity in this study is assessed through the use of surveys, which is International Physical Activity Questionnaire (IPAQ) were used; and also measured with pedometer.[10,11] The use of both IPAQ questionnaire and pedometer were done to objectively measure the physical activity without abandoning the previous routine done by the subjects; moreover, pedometer was only able to measure footwork as a parameter of physical activity.

Numerical data such as patient age were presented with mean, standard deviation, median, and range. Categorical data such as patient gender were presented as frequency and percentage. Distribution of data was assessed with 1-Sample Kolmogorov Smirnov test. IPAQ score is considered as poor shall it is below 600 METS points and is considered good shall it is above 600 METS points. Physical Fitness Index (PFI) was constructed with Harvard Step and heart beat measurement following the Harvard Step Test. The Harvard Step Tes is method that easy to perform in examining the level of physical fitness and aims to improve the cardiac and detection the cardiovascular disease.[12] It is formulated with formula:

$$\text{PFI} = \frac{\text{Duration of Harvard Step Test x 100}}{2 \text{ x } (T1 + T2 + T3)}$$

which T1 stands for heartbeat measured for 30 seconds 1 minute following the step, T2 stands for heartbeat measured for 30 seconds 2 minute following the step, and T3 heartbeat measured for 30 seconds 3 minute following the step. Results was then classified into poor (<55), average (55–64), fair (65–79), good (80–89), and very good (≥90). Pedometer used in this study is Garmin Vivovit 2, and was calibrated prior to use. Pedometer measurement was considered as good shall average of 5-day measurement exceeded 10.000 steps, while average below 10.000 steps will be considered as poor. The relationship between physical activity and fitness level was analyzed by Pearson Correlation test if the data was well distributed and will be analyzed by Spearman Rank test should the data was not well distributed. Differences between variables will be tested with unpaired t-test if the distribution was normal and the Mann-Whitney if the data were not normally distributed. Statistical analysis for categorical data is tested with the chi-square test if the conditions are met, if not met then the Exact Fisher test is used for tables 2x2 and Kolmogorov Smirnov for tables other than 2x2. Analysis of homogeneity of characteristics was analyzed with comparative analysis of sample characteristics. P-value ≤0.05 was statistically significant, and p-value >0.05 was not statistically significant. The data were processed by SPSS version 24.0 for the Windows program.

Results

The total admitted subjects were 100 residents, 6 residents were excluded due to pregnancy and 20 residents were excluded due to overweight BMI, so the complete study was conducted on 74 residents. Overall, the mean age was 30.73±2.372 years with the percentage of subjects being male (75.7%) more than female (24.3%). The majority of subjects had poor physical activity (59.5%) according to IPAQ Questionnaire, compared to good physical activity which was only 40.5%. The majority of subjects had a pedometer measurement in the low category (51.4%), compared to the good category which was only 48.6%. There were 43 (58.1%) subjects with a low level of fitness and 31 subjects (41.9%.) with

Table 1 Subjects' Characteristic

Variable	n=74
Gender	
Male	56(75.7%)
Female	18(24.3%)
Age [b]	
Median	30.00
Range (min-max)	25.00-36.00
BMI (Kg/m^2) [a]	
Mean±Std	24.17±2.758
IPAQ Score [a]	
Low	44(59.5%)
Good	30(40.5%)
Pedometer [b]	
Low	38(51.4%)
Good	36(48.6%)
Fitness Level [a]	
Poor	43(58.1%)
Average	31(41.9%)

Note: Categorical data presented with number/frequency and percentage, while numerical data presented with mean, median, standard deviation and range. [a] data is well distributed. [b] data is not well distributed.

an average level.

IPAQ examination showed that 30 residents had good physical activity and 44 residents had low physical activity. The low physical activity group consisted of 32 male residents (72.7%) and 12 female residents (27.3%). The mean age of the low physical activity group was 30.84±2.542 years with an average BMI of 24.25±2.904. In the good physical activity group, there were 24 (80.0%) male subjects and 6 (20.0%) female subjects. The average age of the good physical activity group was 30.57±2.128 years with an average BMI of 24.05±2.572. The association between BMI, age, sex, and physical activity were conducted to ensure that BMI, age, and sex were not considered as confounding. The association between BMI and physical activity was analyzed by unpaired T-test because data were normally distributed, and the association between age and physical activity was analyzed by the Mann-Whitney test because it was not normally distributed. The results showed a p-value greater than 0.05, thus they were not statistically significant. Categorical data on gender was analyzed by Chi-Square statistical test. The results obtained a p-value greater than 0.05, thus it was not statistically significant and could be concluded had no influence towards to results in this study.

The results of the pedometer examination showed that 36 subjects had good physical activity and 38 participants had low physical activity. In the low pedometer group, there were 31 (81.6%) male subjects and 7 (18.4%) female subjects, with a mean age of 31.08±2.398 years, and a mean BMI of 24.18±3.082. In the good pedometer group, there were 25 (69.4%) male subjects and 11 (30.6%) female subjects, with a mean age of 30.36±2.320 years, and a mean BMI of 24.16±2.414. Data regarding IPAQ Questionnaire score were distributed well, while pedometer measurement was not well distributed. The results of the statistical test for age, BMI, and gender were not statistically

Table 2 Characteristics Based on Physical Activity (IPAQ Score)

Variable	Physical Activity (IPAQ Score) [a]		P value
	Low n=44	Good n=30	
Gender			0.474
Male	32(72.7%)	24(80.0%)	
Female	12(27.3%)	6(20.0%)	
Age [b]			0.689
Median	31.00	30.00	
Range (min-max)	26.00-36.00	25.00–35.00	
BMI [a]			0.758
Mean±Std	24.25±2.904	24.05±2.572	

Note: ** considered as statistically significant with p value <0.05. [a] data is well distributed. [b] data is not well distributed

Table 3 Characteristics Based on Physical Activity (Pedometer)

Variable	Physical Activity (Pedometer) [b]		P-value
	Low	Good	
	n=38	n=36	
Gender			0.224
Male	31 (81.6%)	25 (69.4%)	
Female	7 (18.4%)	11 (30.6%)	
Age [b]			0.195
Median	31.00	30.00	
Range (min-max)	27.00–36.00	25.00–35.00	
BMI [a]			0.977
Mean±Std	24.18±3.082	24.16±2.414	

considered as statistically significant with p value <0.05 [a] data is well distributed. [b] data is not well distributed.

Table 4 Characteristics Based on Fitness Level

Variable	Physical Fitness [a]					P-value
	Poor	Average	Fair	Good	Very good	
	n=43	n =31	n =0	n=0	n=0	
Gender						0.767
Male	32 (74.4%)	24 (77.4%)	0	0	0	
Female	11 (25.6%)	7 (22.6%)	0	0	0	
Age [b]						0.790
Median	31.00	30.00	0	0	0	
Range (min-max)	26.00–36.00	25.00–35.00	0	0	0	
BMI [a]						0.252
Mean±Std	24.48±3.000	23.74±2.361	0	0	0	

** considered as statistically significant with p value <0.05 [a] data is well distributed. [b] data is not well distributed.

significant (p>0.05) thus could be concluded had no influence towards to results in this study.

The results of the examination of the fitness level showed that 43 subjects had low fitness levels and 31 residents had average fitness levels. In the low fitness group, there were 32 (74.4%) male residents and 11 (25.6%), female residents, with mean age of 30.81±2.547 years

Table 5 Fitness Level Based on IPAQ Questionnaire and Pedometer measurement

Variable	Physical Fitness		P value
	Poor	Average	
	n=43	n=31	
Physical Activity			0.0001**
Low	41 (95.3%)	3 (9.7%)	
Good	2 (4.7%)	28 (90.3%)	
Pedometer			0.0001**
Low	30 (69.8%)	8 (25.8%)	
Good	13 (30.2%)	23 (74.2%)	

** considered as statistically significant with p value <0.05

Table 6 Correlation between Physical Activity (Measured with IPAQ Score and Pedometer) and Physical Fitness

Variable	Spearman Rho Coefficient	Sig (two tailed)
IPAQ Score [a]	0.618 [d]	0.000**
Pedometer Measurement [b]	0.315 [d]	0.006**

**considered as statistically significant with p value <0.05
[a] data is well distributed. [b] data is not well distributed [c] correlation test was done with Pearson test [d] correlation test was done with Spearman Rank test

and a mean BMI of 24.48±3.000. In the average fitness level group, there were 24 (77.4%) male subjects and 7 (22.6%) female subjects with a mean age of 30.61±2.140 years and a mean BMI of 23.74±2.361. The results of the statistical test in the research group above obtained a p-value greater than 0.05 for age, BMI, and gender.

In the group of low fitness, the low physical activity with IPAQ Score was 41 (95.3%) and good physical activity was 2 (4.7%). In the group with an average fitness level, the physical activity with IPAQ score was low in 3 (9.7%) subjects and good in 28 (90.3%) subjects. The results of Chi-square tests obtained p<0.05, which means that there was a significant relationship between physical activity by IPAQ Score and fitness level. In this group, the physical activity by pedometer was low in 30 (69.8%) subjects and good in 13 (30.2%) subjects. In the group with an average fitness level, for physical activity by a pedometer, the low category was 8 (25.8%) and 23 (74.2%). The results of Chi-square obtained p <0.05, which means that there was a significant relationship between physical activity by pedometer and fitness level with both measurements done by IPAQ questionnaire (subjectively) and Pedometer (objectively).

Table 6 showed correlation between physical activity and physical fitness. Due to data of PFI and pedometer measurement was not distributed normally, Spearman Rank Correlation was used. Both measurement of physical activity showed significance positive correlation. However, measurement of physical activity by IPAQ score showed moderate correlation while measurement by pedometer showed low correlation according to Guilford Criteria.

Discussion

The study was conducted on 74 residents of the Department of Anesthesiology and Intensive Care at Universitas Padjadjaran. The general characteristics of subjects based on gender, age, and body mass index in the two groups did not show any significant difference. Several factors that may affect the assessment of fitness levels include age, gender, genetics, diet, and a healthy lifestyle. In addition, cardiorespiratory endurance, muscle endurance, muscle strength, body composition, and body flexibility also affect the assessment of fitness levels.[8]

Physical activity by IPAQ score was low in 44 subjects and good in 30 subjects, while on the pedometer test, there were 38 subjects in the low group and 36 subjects in the good group. As both measurement (subjectively and objectively) showed similar statistical significance on physical fitness, it could be concluded that in this study, both measurement had similar reliability in assessing physical activity. However, no specific research was carried out to describe the differences between both measurement cause, but it is hypothesized this may be due to the high work demands. The results of this current study are in accordance with research by Harvard which showed that the physical activity of anesthesiologists and residents of Anesthesiology and Intensive Therapy did not meet the recommended standards.[2, 3]

The results of the current study found that the group of subjects with low physical activity had a lower total score of fitness levels, while subjects with good physical activity had better fitness levels. This is in accordance with a study in India which stated that regular physical activity is an important determinant and predictor of fitness levels.[6] The study in Nigeria also showed that people with regular moderate physical activity associated with better level of fitness.[9] Other study in South Africa showed that physical education students had better fitness than medical students.[13]

Harvard step test used in this study assesses primary cardiorespiratory function. Regular physical exercise was known to improve the cardiorespiratory function which is responsible for VO2 max. People who regularly do regular physical exercise for 6 months can increase VO2 max in general by 15-20%. On the other hand, cardiac output has an important role in meeting oxygen demand. Meanwhile, prolonged activity restriction will result in decreased fitness. Bed rest for 10 days will reduce VO2 max by 15% and

27% in 3 weeks.[14, 15] In this study, however, fitness level was only assessed on the cardiorespiratory level and was not tested on the level of muscular endurance. Muscular endurance is another important component to assess fitness level, in which increased exercise intensity will increase tolerance to lactate levels produced by muscles.

Assessment of physical activity can be done using a subjective assessment by IPAQ, while an objective assessment can be done by counting steps using a pedometer. IPAQ score over 600 METS and daily walking steps over 10,000 steps/ day are considered good physical activity. Not all study participants with good IPAQ scores and physical activity based on good pedometers have good fitness levels, but most of the results of IPAQ and pedometer scores show in-line results. This may be due to the subjective nature of the IPAQ assessment which may affect the accuracy of the study. The objective assessment of physical activity carried out in this study, however, was only limited to footwork, while the activities, in reality, may include pushing or moving patient gurneys and monitoring equipment, as well as moving patients to and from the operating table, which might not be differentiated by pedometer measurement.[2,3] It might be also became the reason on how IPAQ questionnaire had better correlation with fitness level compared with pedometer on assessing physical fitness level.

The limitation of this study is the subjective nature of the IPAQ questionnaire, and the installation of a pedometer on the wrist may include hand movement which can cause a bias in the study. Assessment of fitness level using the Harvard step test is more focused on cardiorespiratory function, while other components of fitness levels such as components, such as muscle endurance, muscle strength, body composition, and body flexibility should be considered.

In conclusion, physical activity is well-correlated with physical fitness index. This study also portray on how the physical fitness level of Anesthesiology and Intensive Care residents with good physical activity were better than residents with low physical activity. Further research with other objective measuring instruments and other methods to assess the level of fitness, including the psychological status of the subject is required.

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Effect of Hypervirulent Strains, Antibiotic Resistance, and Host Characteristics on Mortality of *Klebsiella pneumoniae* Bacteremia Patients at a Tertiary Referral Hospital in Denpasar, Indonesia

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Abstract

Klebsiella pneumoniae bacteremia is one of the leading causes of sepsis that has a high mortality rate. The effect of multidrug resistance and different virulence of *Klebsiella pneumoniae* on mortality is still controversial. This study aimed to determine the impact of hypervirulent K. pneumoniae (hvKp), MDR, and clinical characteristics on mortality of *K. pneumoniae* bacteremia patients. A retrospective cross-sectional study was conducted on *K. pneumoniae* bacteremia cases of patients hospitalized at Professor dr. I.G.N.G Ngoerah General Hospital from December 1, 2020, to May 31, 2021. A positive PCR of *rmpA, iucA* genes, and/or a positive string test was identified as hvKp. The mortality rate of 51 K. pneumoniae bacteremia patients samples (aged 0–74 years) was 72.5%, in which 9.8% (5/51) of them were hvKp and 51% of the isolates (26/51) produced the Extended Spectrum Beta Lactamase (ESBL). Furthermore, 9.8% (5/51) of the cases were carbapenem-resistant. Thus, hvKp, MDR, gender characteristics, and comorbidities do not significantly affect the mortality of *K. pneumoniae* bacteremia patients. Multivariate logistic regression analysis showed that sepsis (odds ratio (OR) 4.29; p=0.038) and adult age group (mean 50 years) (OR 3.75; p=0.039) are independent predictors with a significant effect on mortality of *K. pneumoniae* bacteremia patients. Careful and integrated management of *K. pneumoniae* bacteremia patients is essential for better outcomes, especially in sepsis and elderly patients. Although hvKp prevalence is low, emerging MDR-hvKp in health facilities is a severe concern for further actions and research.

Keywords: Bacteremia, *Klebsiella pneumoniae*, mortality, multidrug resistance, sepsis

Introduction

Sepsis is a significant cause of death from infectious diseases, especially if it is not detected early or appropriately treated.[1] *Klebsiella pneumoniae* bacteremia is one of the main etiologies of sepsis and is highly prevalent in Asia and the Middle East.[2] According to a preliminary study by Professor dr. I.G.N.G. Ngoerah Hospital In 2019, there were 177 cases of sepsis with a mortality rate of 74.57%, where *K. pneumoniae* was the most isolated gram-negative bacteria, with 18.54% of all blood culture results (*unpublished data*).

Klebsiella pneumoniae is an opportunistic pathogen and often causes bacteremia and sepsis, both obtained from hospitals and the community, and also has been associated with some common underlying conditions such as elderly patients, patients with diabetes, malignancy, end-stage renal failure, and suppression of the immune system.[3,4] *Klebsiella pneumoniae* has many virulence factors such as capsules, lipopolysaccharide, fimbriae, and siderophores and also its ability to produce an Extended Spectrum of Beta-Lactamase (ESBL) enzyme that causes resistance to many antibiotics, especially third-generation cephalosporins,

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and monobactams.[4] Hypercapsular virulence factors and siderophore aerobactin biosynthesis of hypervirulent *Klebsiella pneumoniae* (hvKp) have an essential role in the pathogenesis of *K. pneumoniae* invasive bacteremia infection and have an impact on patient outcomes.[5]
The presence of hypermucoviscosity (*rmpA*) and aerobactin (*iucA*) genes are closely related to morbidity and mortality as well as an accurate molecular marker of hvKp infection both epidemiologically and clinically experimentally and in murine sepsis models.[5] A study in China showed that several cases of Multidrug-resistant (MDR) hvKp bacteremia patients, including carbapenems, had poor clinical outcomes in septic shock and death.[6,7]

The increasing numbers of hvKp bloodstream infections and the high rate of MDR *K. pneumoniae* in Asia are concerns about the impact, including in Indonesia. Until now, the study of hvKp bacteremia in Indonesia is limited. This study aimed to determine the prevalence of hvKp and analyze the effect of hypervirulent strains, MDR *K. pneumoniae*, demographic characteristics, and patient comorbidities on mortality of *K. pneumoniae* bacteremia patients.

Methods

This research was conducted with 51 consecutive cases of *K. pneumoniae* bacteremia between December 1, 2020, and May 31, 2021, collected from patients hospitalized at Professor dr. I.G.N.G. Ngoerah Hospital, a tertiary teaching hospital in Denpasar, Bali, Indonesia. This retrospective cross-sectional study included only the first bacteremia episode for each patient. Patient characteristics, including age, sex, underlying disease (comorbidity), clinical features, and outcome, were evaluated. The study was approved by the Ethical Research of Udayana University, Indonesia (Number 1236/UN14.2.2.VII.14/LT/2021). The need for written informed consent was waived owing to the study's retrospective nature.

Klebsiella pneumoniae bacteremia was defined as one or more positive blood cultures of *K. pneumoniae* in patients with clinical signs of infection, such as fever, shaking chills, and sweats, with or without local signs and symptoms.[8] Multidrug-resistant (MDR) *K. pneumoniae* was defined as the resistance of *K. pneumoniae* to at least one of three different classes of antibiotics or more as seen from the results of antibiotic sensitivity tests.[9] Comorbidities were underlying diseases that have been diagnosed in patients other than bloodstream infections (bacteremia) in this case centered on critical illnesses in the central nervous system, cardiovascular, respiratory, digestive, urogenital, endocrine, musculoskeletal, malignancies and immune system disorders. Sepsis was defined as organ dysfunction characterized by more than or same as 2 of Sequential Organ Failure Assessment (SOFA) scores or more than or same as 7 of PELOD-2 scores (0–18 years old patients) or clinically and laboratory diagnosed sepsis recorded in the patient's medical record, as a result of bloodstream infection (bacteremia) *K. pneumoniae.* The medical record data for SOFA/PELOD-2 scores and the diagnosis of sepsis used were between 48 hours before and after taking blood culture specimens identified as *K. pneumoniae.* The thirty-day mortality rate was defined as the clinical outcome of dying from *K. pneumoniae* bacteremia patients in the care of patients at Professor dr. I.G.N.G. Ngoerah Hospital within a period of up to 30 days from the day of taking positive blood culture specimens reviewed from the patient's medical record.[10]
Identification and antimicrobial susceptibility testing of *Klebsiella pneumoniae* blood isolates were performed by using Vitek 2 Compact system (bioMerieux, Marcy l'Etoile, France). MICs results were interpreted according to the 2020 Clinical and Laboratory Standards Institute (CLSI, M100-S27) breakpoints. The production of ESBL was screened by measuring the MICs of cefotaxime, ceftazidime, and aztreonam that were automatically defined by the Vitex 2 Compact system. Carbapenem-resistant *K. pneumoniae* was described as being resistant to meropenem or ertapenem. All *K. pneumoniae* isolates were cultured on blood agar plates, incubated for 24 hours at 37°C, and subjected to a string test. Using an inoculation loop, a positive string test was defined as bacterial colonies on a blood agar plate stretching for >5 mp.[11] DNA was extracted from bacterial colonies using a plasmid DNA extraction kit (QIAprep® Spin Miniprep Kit, Qiagen, Gmbh) following the manufacturer's instructions. Uniplex PCR was performed to detect hypervirulent *K. pneumoniae* (hvKp) biomarker genotypes such as *p-rmpA* and *iucA* genes with primer sets, as shown in Table 1.

The final concentration of the primer set was ten µM each. PCR cycles of *p-rmpA* consisted of pre-denaturation at 94°C for 4 minutes; 30 cycles of denaturation at 94°C for 30 seconds, primer annealing at 50°C for 40 seconds, and extension at 72°C for 1 minute; and a final extension at 72°C

Table 1 Primer Sets Used for Identification of hvKp

PCR Target	Primer Sequence (5'- 3')	Size (bp)	Reference
$_p$rmpA	F: ACTGGGCTACCTCTGCTTCA	366	12
	R: CAGTAGGCATTGCAGCA		
iucA	F: CGCTTCACTTCTTTCACTGACAGG	239	5
	R: AATCAATGGCTATTCCCGCTG		

PCR=polymerase chain reaction; bp = base pairs; hvKp = hypervirulent *k. pneumoniae*

for 10 minutes.[12] PCR cycles of *iucA* consisted of pre-denaturation at 95°C for 2 minutes; 30 cycles of denaturation at 95°C for 30 seconds, primer annealing at 55°C for 43 seconds, and extension at 72°C for 1 minute; and a final extension at 72°C for 10 minutes (MiniAmp™ thermal cycler, Applied Biosystems™).[5] Hypervirulent *K. pneumoniae* (hvKp) was defined by biomarker that contain at least 2 of 3 phenotypic and genotypic markers, including positive string test, detectable hypervirulent *rmpA* and *iucA* gene.

Data were input and processed using Microsoft Excel 2019, and descriptive statistics were calculated. Data analysis used SPSS statistic 25.0 (USA, IBM analytics). The bivariate chi-square or Fisher's exact test assessed significant associations and effects between two categorical variables. Multivariate logistic regression was used to identify risk factors for *K. pneumoniae* sepsis and independent predictors of 30-day mortality. All variables were included in the multivariate model in a forward stepwise approach using the likelihood-ratio test. The chi-square test showed that the association measure was an odds ratio (OR) while the logistic regression was an adjusted odd ratio (OR). The inference process based on a 95% Confidence Interval of OR and *p-value* < 0.05 were considered statistically significant.

Results

During the study period, 51 patients were identified as *K. pneumoniae* bacteremia, and 5 of 51 *K. pneumoniae* isolates (9.8%) were identified as hvKp strains. All hvKp isolates positive for *rmpA* and/or *iucA* genes have positive string tests. The general characteristics of *K. pneumoniae* bacteremia patients are shown in Table 2. The adult group (>18 years old) was dominant in this study (58.8%), and diabetes and gastrointestinal abnormality were the most frequent underlying diseases. The proportion was no significant difference in sex, age group, comorbidity, incidence of sepsis, and mortality in the different strains of *K. pneumoniae.* In this study, it was found that all hvKP isolates were not ESBL-producer. In addition, no MDR or carbapenem-resistant were found in the hvKP

Table 2 General Characteristics of *Klebsiella pneumoniae* Bacteremia Patients

Variable	n (%) (n=51)
Age groups	
0–1 years old	17 (33.4)
1–18 years old	4 (7.8)
>18 years old	30 (58.8)
Male	25 (49)
Female	26 (51)
Comorbidities	37 (72.5)
Low birth weight and preterm infants	10 (19.6)
Diabetes	9 (17.6)
Gastrointestinal abnormality	7 (13.7)
Cardiovascular disease	4 (7.8)
Malignancy	3 (5.9)
Chronic kidney disease	2 (3.9)
Immunocompromise (AIDS)	2 (3.9)
hvKp	5 (9.8)
cKp	46 (90.2)
MDR-*K. pneumoniae*	31 (60.8)
ESBL *producer K. pneumoniae*	26 (51)
Carbapenem-resistant *K. pneumoniae*	5 (9.8)
Sepsis/shock septic	37 (72.5)
Mortality	37 (72.5)

n=total sample; hvKp=Hypervirulent *K. pneumoniae;* cKp =Classical *K. pneumoniae*

Table 3 Patient Characteristics of Hipervirulent *Klebsiella pneumoniae* bacteremia

Characteristics	hvKp (n=5)	cKp (n=46)	p-value
Sex			
Male	3 (60%)	22 (47.8%)	0.668
Female	2 (40%)	24 (52.2%)	
Age			
More than 18 years old	5 (100%)	25 (54.3%)	0.069
0-18 years old	0 (0%)	21 (45.7%)	
With comorbidities	4 (80%)	33 (71.7%)	1.000
Antibiotics resistance			
ESBL	0 (0%)	26 (56.5%)	0.023*
MDR	0 (0%)	31 (67.4%)	0.007*
Carbapenem resistant	0 (0%)	5 (10.9%)	1.000
Sepsis/Septic shock in infection onset	4 (80%)	33 (71.7%)	1.000
30-day mortality	5 (100%)	32 (69.6%)	0.305

*Statistically significant, p<0.05; hvKp-BSI=hypervirulent *k. pneumoniae*-bloodstream infection; cKp-BSI=classical *k. pneumoniae*-bloodstream infection; ESBL=extended spectrum beta-lactamase; MDR=multidrug-resistant

of males and females was mostly similar, with 49% and 51%, respectively. Most of the isolates were classical strains of *K. pneumoniae* (cKp) (90.2%), which tended to have ESBL-producing (51%) and carbapenem-resistant *K. pneumoniae* (9.8%) compared to hvKp strains.

The patient characteristics with hvKp and cKp bacteremia are shown in Table 3. There

Table 4 Antibiotic Susceptibility of *K. Pneumoniae* Bacteremia Isolates

Antimicrobial Agents	hvKp (n=5)	cKp (n=46)	p-value
Ampicillin-sulbactam	5 (100%)	14 (30.4%)	0.005*
Piperacillin-tazobactam	5 (100%)	32 (69.6%)	0.305
Cefazolin	5 (100%)	13 (28.3%	0.004*
Cefuroxime	5 (100%)	15 (32.6%)	0.007*
Ceftriaxone	5 (100%)	16 (34.8%)	0.009*
Ceftazidime	5 (100%)	17 (37%)	0.011*
Cefepime	5 (100%)	30 (65.2%)	0.167
Cefoperazone	5 (100%)	15 (32.6%)	0.007*
Cefoperazone-sulbactam	5 (100%)	15 (32.6%)	0.007*
Aztreonam	5 (100%)	16 (34.8%)	0.009*
Ertapenem	5 (100%)	41 (89.1%)	1
Meropenem	5 (100%)	41 (89.1%)	1
Gentamicin	5 (100%)	27 (58.7%)	0.143
Amikacin	5 (100%)	33 (71.7%)	0.311
Levofloxacin	4 (80%)	18 (39.1%)	0.152
Ciprofloxacin	4 (80%)	16 (34.8%)	0.071
Trimethoprim-sulfamethoxazole	5 (100%)	20 (43.5%)	0.023*

*Statistically significant, *p*<0.05; hvKp=Hypervirulent *K. pneumoniae;* cKp=Classical *K. pneumoniae*

Table 5 Clinical and Microbiological Characteristics Associated with 30-Day Mortality of Klebsiella pneumoniae Bacteremia Patients

Variable	Mortality		OR (95% CI)	p-value
	Death (n=37)	Survivors (n=14)		
Sex				
Male	21 (56.8%)	4 (28.6%)	3.281 (0.868–12.400)	0.072
Female	16 (43.2%)	10 (71.4%)		
Age groups				
>18 years old	25 (67.6%)	5 (35.7%)	3.750 (1.030–13.648)	0.039*
0–18 years old	12 (32.4%)	9 (64.3%)		
Comorbidities				
Present	27 (73%)	10 (71.4%)	1.080 (0.275–4.241)	1.000
Absent	10 (27%)	4 (28.6%)		
K. pneumoniae strain				
hvKp	5 (13.5%)	0 (0%)	-	0.305
cKp	32 (86.5%)	14 (100%)		
Antibiotic resistance				
ESBL	18 (48.6%)	8 (57.1%)	0.711 (0.206–2.454)	0.588
MDR	21 (56.8%)	10 (71.4%)	0.525 (0.139–1.984)	0.338
Carbapenem-resistant	3 (8.1%)	2 (14.3%)	0.529 (0.079–4.562)	0.606
Sepsis/septic shock	30 (81,1%)	7 (50%)	4.286 (1.131–16.238)	0.038*

*Statistically significant, $p<0.05$; OR (95% CI)=Odd Ratio (95% Confidence Interval); hvKp=Hypervirulent *K. pneumoniae;* cKp=Classical *K. pneumoniae;* ESBL=Extended Spectrum Beta Lactamase; MDR=Multidrug-Resistant

isolate. ESBL-producing and MDR *K. pneumoniae* were significantly identified in more cKp isolates (26/46, 56.5%) than in hvKp isolates (0%) (p<0.05). The incidence of sepsis in hvKP bacteremia was found to be 80% (4/5) with a 100% (5/5) mortality rate, but this was not statistically significant if compared with cKP-BSI (p=0.305) (Table 3).

Hypervirulent *K. pneumoniae* isolates were significantly susceptible to ampicillin-sulbactam, cefazolin, cefuroxime, ceftriaxone, ceftazidime, cefoperazone, cefoperazone-sulbactam, aztreonam, and trimethoprim-sulfamethoxazole than cKp (Table 4).

Table 5 showed that gender and host comorbidities, hypervirulent strains, and antibiotic resistance of *K. pneumoniae* did not show a statistically significant relationship or effect on mortality in *K. pneumoniae* bacteremia patients (p >0.05).

The variables of the adult age group and the incidence of sepsis showed a significant relationship and effect on the mortality of *K. pneumoniae* bacteremia patients (p<0.05).

Table 6 Multivariate Logistic Regression Analysis of Predictive Factors that Influence 30-day Mortality of *Klebsiella pneumoniae* Bacteremia Patients

Outcome	Variable	Adjusted OR 95% CI	P value
Sepsis/septic shock	Male sex	1.592 (0.441–5.747)	0.478
	Comorbidity present	1.919 (0.488–7.548)	0.351
30-day mortality	>18 years old group	4.272 (1.060–17.224)	0.041*
	Sepsis/septic shock	4.901 (1.164–20.635)	0.030*

*Statistically significant, $p<0.05$; OR=Odd Ratio; CI=Confidence Interval

Multivariate analysis further demonstrated that the adult group (>18 years old patients) (OR=4.272) and sepsis/septic shock (OR=4.901) at infection onset were independent predictors for 30-day mortality in patients with *K. pneumoniae* bacteremia (Table 6).

Discussion

Sepsis is a life-threatening organ dysfunction caused by the failure of the patient's response to an infection characterized by severe systemic inflammation in response to the spread of infectious pathogens.[1]morphology, cell biology, biochemistry, immunology, and circulation The mortality and incidence of sepsis in *K. pneumoniae* bacteremia in this study was relatively high compared to previous studies, which were 15-48%.[10,13] To reduce the high incidence of sepsis and mortality of *K. pneumoniae* bacteremia at Professor dr. I.G.N.G. Ngoerah Hospital, adequate management of bacteremia patients is required, starting from diagnostics, appropriate empirical and definitive antibiotic therapy, and preventing the spread of MDR *K. pneumoniae* and hvKp strain.

The hvKp bacteremia prevalence in this study was lower than in other studies from Asian countries such as China (46%), Korea (42.2%), and Taiwan (41.9%).[14,15] However, the prevalence of this study was not much different from that in Algeria (9.2%) and Spain (10.7%).[12,16] Several previous studies showed the endemic spread of hvKp infection in East Asian countries, especially in Taiwan, Korea, and China, which have the same geographical and ethnic characteristics. Hence, the prevalence of hvKp is higher than that in this study. In addition, the research conducted in these East Asian countries has a large and multicenter sample size compared to this study. At the same time, the similarity of the prevalence rates of this study with the prevalence in Algeria and Spain could be due to the similarity of the population of the study samples, which were both carried out in tertiary referral hospitals which did not reflect community infection. Nonetheless, in several case reports in Western countries, hvKp infection often occurs in Asian ethnicities. This data suggests that Asians may be more susceptible to hvKP infection than other ethnic groups.[14]

This study found that hvKp strains tend to be sensitive to many antibiotics and do not produce ESBL and Carbapenemase. These findings were not much different from other studies.[3,17]This is because of majorly hvKp in community infection that tends to less exposure to multiple antibiotics and hospital care. According to the genomic study of Lam et al. in 2018, it was speculated that hvKp is a hypercapsular expression that acts as a barrier to the transformation and conjugation of antibiotic resistance genes and also the CRISPR/Cas system that blocks foreign DNA from entering hvKp cells.[18] However, in the study by Zhang et al. in 2016, it was shown that there were Carbapenem-resistant hvKp strains of 7.4% of all patient specimens in two hospitals in China with poor outcomes.[6]Based on the study of a hospital in China, Shen et al. in 2019 also showed that MDR-hvKp was carrying the blaCTX-M ESBL resistance gene and hypervirulence gene (*rmpA* and *rmpA2*) on the same hybrid plasmid, plasmid p11492-vir-CTXM, in *K. pneumoniae* bacteremia patients with pancreatic abscess with sepsis and death outcome.[7] This indicates that emerging MDR-hvKp in tertiary referral hospitals is becoming a concern that requires vigilance and further elucidation.

In the present study, hvKp did not have a significant relationship and influence on the incidence of sepsis and mortality in *K. pneumoniae* bacteremia patients. The different results obtained from the multivariate analysis of research by Togawa et al. in 2015 showed that hvKp had 15 times more effect on the risk of sepsis compared to cKp (OR=15.92) but had no effect on mortality,[19] as found in this study. Meanwhile, research by Harada et al. in 2019 showed that hvKp strain was a risk factor for the incidence of sepsis (RR=1.55) and mortality (RR=1.25).[20] The effect of hypervirulent strain from these studies is still controversial on the outcome of sepsis and mortality. Previous studies reported that other comorbid cofactors were more influential in mortality than hvKp in bacteremia.[8,21] Similar findings were also observed in this study that bacteremia events were dominantly found with comorbidities. The sample of patients with hvKp bacteremia in this study had an average age of 49 years, one of which was without comorbidities. All of them had sepsis and death, but due to the prevalence of hvKp bacteremia being low compared to cKp, it did not show a statistically significant effect on the incidence of sepsis and mortality.

The overproduction of polysaccharide capsules (hypermucoviscosity) in hvKp strains plays a role in the resistance mechanism to complement and anti-phagocytosis against neutrophils and macrophages.[4] Furthermore, the virulence factor siderophore aerobactin

also has a role in the pathogenesis of bacteria to cause more severe bacteremia. Aerobactin siderophore, which has a greater affinity for iron than host transport proteins, can take up free iron in host plasma and make it easier to multiply and spread.[15] Therefore, hvKp has a high invasive tendency from foci of infection, including rapidly causing bacteremia, multiple organ abscesses, metastatic infections such as endophthalmitis, meningitis, and pneumonia, which are associated with high mortality and consequently challenging to approach therapy.[4,11] The higher mortality in bacteremia by hvKp strains compared to cKp is related to bacterial virulence factors, including capsule strain K2 and the presence of the *rmpA* gene compared to comorbid host factors.[8]

Due to the limited choice of antibiotics that effectively manage MDR *K. pneumoniae* infections, such infections have a higher morbidity and mortality rate than non-MDR bacterial infections.[4] According to Xu et al., adult patients (>18 years) showed that carbapenem-resistant *K. pneumoniae* bacteremia provided a significant mortality risk of 2 times compared to carbapenem-sensitive ones.[17] Whereas, in the pediatric and neonatal patient population, patients with sepsis caused by MDR had a significantly higher risk than non-MDR.[22] However, different things were found in this study. There was no difference in the proportion and significant effect of antibiotic resistance (ESBL and carbapenem resistance) on the incidence of sepsis and mortality. This study is not much different from the results of research by Namikawa et al., where there was no significant difference and effect between ESBL-producing *K. pneumoniae*, AmpC, and carbapenemase on the mortality of *K. pneumoniae* bacteremia patients.[13] This could be due to the influence of other variables such as comorbidity, suitability, and appropriateness of empirical antibiotic administration in *K. pneumoniae* bacteremia patients.

Neonates and the elderly have a higher risk of *K. pneumoniae* infections than other age groups.[4] It is not much different from this study that the proportion of *K. pneumoniae* bacteremia was more prevalent in the adult patient group (>18 years) aged 26–74 years. This finding showed that the older age has a higher risk of bacteremia. The study of Namikawa et al. (2019) also showed that the risk of death from *K. pneumoniae* bacteremia in the elderly (median age 66.5 years) was significantly higher than in other age groups.[13] It was also shown in this study that the predominant adult age group was the elderly, which significantly affected the mortality of *K. pneumoniae* bacteremia patients. In older people, there is a decrease in the differentiation and repopulation of lineage cells of the immune system, such as dendritic cells, natural killer (NK) cells, neutrophils, macrophages, and lymphocytes. Increasing age also decreases the function of adaptive immune cells of B lymphocytes and T lymphocytes. B lymphocyte cells experience a decrease in the number and function of antibody secretion, IL-2, and class switch recombination of antibodies. Meanwhile, T lymphocytes decreased lymphopoiesis, naive T cells, mitogen-associated proliferation, signal transduction, CD28 expression on CD8+ T cells, and decreased membrane receptors. In older people, there is also an increase in the level of pro-inflammatory cytokines such as IL-6 and TNF-α, acute phase reactants such as CRP, and clotting factors, referred to as inflammatory. Manifestations of a decrease in the immune system can facilitate the occurrence of severe infections such as bacteremia from opportunistic pathogenic bacteria such as cKp, which is dominant in this study. The effect of inflammatory aging is closely related to the risk of mortality in elderly patients.[23]

In contrast to hvKp strains which can cause a primary infection in patients, cKp strains can cause serious infections such as pneumonia, bacteremia, or meningitis in immunocompromised individuals, including people suffering from diabetes or malignancies.[4] Bacteremia infection in this study was caused mainly by cKp infection (90.2%), most of whom had comorbidities (72.5%). The bivariate chi-square test did not show a statistically significant difference in influencing the incidence of sepsis and patient mortality. However, the multivariate analysis with logistic regression found a tendency for the influence of comorbid variables on the incidence of sepsis, although not statistically significant. This is because the dependent variable of sepsis is the outcome variable of infection, where all patient samples have homogeneous characteristics, namely bacteremia infection. Patients with diabetes mellitus and malignancy have innate immune system reduction.[4] Failure of the defense function against bacteria, including decreased production of chemokines and cytokines, decreased response, and phagocytic ability of neutrophils, occurs in patients with comorbid diabetes mellitus. This condition is caused by changes in glucose metabolism and oxidative stress in patients with diabetes mellitus.[24] Decreased

function of the natural immune system in patients with malignancy can be caused by chemotherapy's cytotoxic effect, killing immune cell division rapidly and causing neutropenia conditions.[4] In the neonates, especially in premature infants, the risk of an immature immune system, the absence of gastrointestinal microbiota, and an increase in the permeability of the gastrointestinal mucosa facilitate the spread of gastrointestinal pathogenic microbes such as cKp.[25]

Patients with *K. pneumoniae* bacteremia who had fallen into sepsis had a higher mortality risk of 4.9 times than those without sepsis (adjusted OR=4.901) in this study. This study is in line with previous studies where sepsis was a risk factor for mortality in *K. pneumoniae* bacteremia patients.[10,13,17,19] Sepsis in bacteremia is a severe systemic inflammation in response to the spread of infection and pathogenic virulence factors and or an uncontrolled hyperinflammatory response mediated by the release of various pro-inflammatory mediators due to host factors. Sepsis, characterized by organ failure due to endothelial dysfunction and global tissue hypoxia, presents a very high mortality risk.[1]

This study had several limitations. First, this study had a relatively narrow population in only one tertiary referral hospital, thus providing a selection bias where in this study, most of the cKp strains were MDR. Second, this study was conducted on a population of all ages, from neonates to the elderly, with heterogeneous characteristics that cannot be generalized. Third, this study design was a retrospective cross-sectional study with a limited number of variables analyzed and is not longitudinal, so the number of samples that can be reached is only the minimum number of statistical calculations required. The limitations of retrospective data collection in this study include several things, including firstly, the large number of patient samples that were not subjected to culture other than blood cultures, so it is complicated to determine the source of invasive infection or metastasis from hvKp strains; the second is the existence of operational biases such as confounding variables that cannot be controlled due to data limitations such as the severity of sepsis (SOFA/PELOD-2 and APACHE scores) that affect the results of data analysis, especially the effect of comorbidities on sepsis and mortality. Further prospective research with an appropriate and longitudinal research design is needed to validate the results of this study.

In conclusion, using a retrospective single-center study of patients with *K. pneumoniae* bacteremia, our study demonstrated that the adult age group (>18 years old) with elderly dominance and sepsis/shock septic were independent risk factors associated with *K. pneumoniae* bacteremia mortality. Although hvKp strain was not significantly impacting 30-day mortality in this study because of the low prevalence, finding and high mortality of hvKp strain in tertiary hospital settings with high MDR prevalence is a severe concern for further action and research.

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Etiology and Antifungal Sensitivity Test in Otomycosis Caused by *Candida* Sp.

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Abstract

Otomycosis is a common fungal infection of the external auditory meatus frequently diagnosed in otolaryngology outpatient clinics. Resistance to antifungals is currently a significant concern, with intrinsic and acquired resistance increasing among isolates that cause fungal infections. The purpose of this research was to identify *Candida* species causing otomycosis and determine the pattern of antifungal susceptibility among these *Candida* species. A prospective study was conducted in the Margono Soekarjo General Hospital and Department of Microbiology, Faculty of Medicine, Universitas Jenderal Soedirman Purwokerto, Indonesia, from April–September 2022. Forty-seven (47) clinical samples of otomycosis were collected from 41 patients and then isolated bedside on fungal culture media and was prepared on an object glass for direct microscopic examination of the specimens. Fungal identification was performed using 10% potassium hydroxide (KOH) to observe fungal elements. Samples were cultured on Saboraud dextrose agar (SDA) media with chloramphenicol and Czapek dox agar. The Germ Tube Test was used to identify *Candida* while yeast-specific identification and antifungal susceptibility assay using a rapid commercial kit was applied for specific identification of the fungus. Antifungal susceptibility patterns were obtained using the Integral System Yeast Plus (ISYP) media pack. *Candida* parapsilosis was the most prevalent *Candida* species discovered in this study, accounting for approximately 41.66%, which was followed by *Candida tropicalis* (25%) and *Candida krusei* (12.5%), whereas Candida albicans only accounted for 4.1% of the specimens. All Candida species were sensitive to flucitosine and ketoconazole, whereas the voriconazole sensitivity rate reached 96%. This study concludes that *Candida parapsilosis* is the most prevalent species of *Candida* in otomycosis, and that all Candida species are sensitive to Flucitosine, ketoconazole, and voriconazole.

Keywords: Antifungal sensitivity test, *candida*, otomycosis

Introduction

Otomycosis is a common infection of the external auditory meatus caused by a fungus that is frequently diagnosed in otolaryngology outpatient clinics. This disease is commonly encountered in nations with tropical and subtropical climates, with air humidity between 70 and 80 percent and air temperature between 15 and 30 degrees Celsius. The worldwide prevalence of Otitis Externa with otorrhea is roughly 9 to 30%.[1,2]

Warm and humid weather, external bacterial otitis, swimming, close or continuous contact with water; eczema, seborrhoeic dermatitis of the outer ear; external ear injury due to a foreign object; wearing headphones, anatomical disorders, diabetes mellitus, and immune deficiency are risk factors for otomycosis.[3]

Multiple types of fungi can cause otomycosis. *Aspergillus niger* and *Candida albicans* are the two fungi most associated with otomycosis.[4,5] Patients with otomycosis typically complain of itching, otalgia, a feeling of fullness in the ear, tinnitus, hearing loss, a sensation of congestion, and ear discharge.[6] Although otomycosis is not life-threatening, it can be frustrating for patients and physicians due to its long-term treatment requirements and high recurrence rate.[7]

Resistance to antifungals is currently a significant concern, with intrinsic and acquired resistance increasing among isolates causing

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fungal infections. Multiple reports of antifungal resistance among isolates from patients with fungal otitis.[8] Indonesia has a tropical climate, which may influence the incidence of otomycosis. However, a literature search reveals little about otomycosis regarding the type of fungus and antifungal sensitivity to the otomycosis-causing fungus. This study aims to identify Candida species and determine the pattern of antifungal susceptibility among Candida species that cause otomycosis.

Methods

A cross-sectional study was conducted in the Otorhinolaryngology Clinic at Margono Soekarjo Hospital and Department of Microbiology Faculty of Medicine Universitas Jenderal Soedirman Purwokerto, Indonesia, from April to September 2022. The study was approved by the Health Research Ethics Committee at the Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto (018/KEPK/PE/II/2022). The inclusion criteria for this study were patients with a clinical diagnosis of otomycosis, a minimum age of 17 years old, and written informed consent to participate. This study excluded patients with severe otitis externa and those who were uncooperative. Data were then tabulated for analyses using SPSS version 24.0 for the Windows program.

Clinical samples were collected by swabbing ear discharge, which ranged in color from white to black, using a sterile flexible mini-flocked swab (Copan, Italy). The sample was then isolated bedside on fungal culture media and in object glass for direct microscopic examination of specimens, then transferred to the Microbiology Laboratory Faculty of Medicine Universitas Jenderal Soedirman. Fungal identification was carried out using 10% KOH to observe fungal elements, including hyphae, spores, budding yeast, and yeast with pseudohyphae.

The samples were grown in an aerobic environment for four weeks on SDA media supplemented with chloramphenicol (Himedia, Mumbai, India) and Czapek dox agar (Himedia). Cultures are checked every 3-5 days. Fungal cultures must be incubated for at least 30 days before being judged negatively. Identification was carried out based on colony morphology and microscopy with Lactophenol cotton blue (LPCB). Candida was identified by a germ tube test using colonies inserted in serum, incubating for 1-2 hours at 37°C, and observing the presence of germination without restriction in *Candida albicans.*

Yeast-specific identification and antifungal susceptibility assay using rapid commercial kit Specific identification and four antifungal susceptibilities patterns were obtained using Integral System Yeast Plus (ISYP) commercial equipment (Liofilchem, Italy), according to the manufacturer's instructions. Briefly, Candida conidial suspension was prepared from 24h new culture on Sabouraud dextrose agar (Merck, Germany) at 35°C. The cell density was adjusted to 0.5 McFarland standard and inoculated to 12 microwells containing dried sugar. Thirteen wells had chromogenic substrate; then, the suspension was subjected to thedilute and released into subjected antifungal wells. The following antifungal concentrations were utilized at the end of the experiment: Nystatin (1.25 g/mL), Amphotericin B (2.0 g/mL); 5-Fluorocytosine (16.0 g/mL); Econazole (2.0 g/mL), Ketoconazole (0.5 g/mL), Clotrimazole (1.0 g/mL), Miconazole (2.0 At the time, the 24th well was used as a gauge. The wells, except well thirteen, were covered with a drop of Vaseline oil. The microplates were incubated at 36±1 °C for 48 hours, and the color shift was read. Sugar assimilation patterns were analyzed, a code was generated, and the corresponding species was located using this method. The *Candida albicans* ATCC 24433, *C. glabrata* CBS 138, and *C. krusei* ATCC 6258 were quality controls.

Results

This study collected 47 samples of otomycosis from 41 patients, of whom 6 (12.76%) had a bilateral infection. Patients with male sex were more common among the 47 samples (51.1% versus 48.9% for females). The age ranges 36 to 40 years and 56 to 60 years account for 14.9% of the population. This study also determined that the right ear is more susceptible to otomycosis than the left (59.6%: 40.4%), according to Table 1.

In the present study, a total of 47 specimens were obtained from 41 patients diagnosed with otomycosis, comprising 35 cases of unilateral and 6 cases of bilateral involvement. Among the 56 isolates cultured, 38 were identified as single infections, while 18 exhibited mixed infections.

Table 2 contains descriptions pertaining to the number and type of candida species. *Candida parapsilosis* was the most prevalent Candida species discovered in this study, accounting for

Table 1 Characteristics of Patients with Otomycosis

Characteristics	Number	Percentage
Sex		
Men	24	51.1
Women	23	48.9
Age (in years)		
16–20	5	10.6
21–25	1	2.1
26–30	9	19.1
31–35	5	10.6
36–40	7	14.9
41–45	2	4.3
46–50	5	10.6
51–55	2	4.3
56–60	7	14.9
61–65	2	4.3
65–70	1	2.1
71–75	1	2.1
Site of ear		
Right ear	28	59.6
Left ear	19	40.4
Unilateral	35	74.3
Bilateral	6	12.7

approximately 41,66%, followed by *Candida tropicalis* at 25% and *Candida krusei* at 12.5%, whereas *Candida albicans* accounted for only 4.1%. (Table 2).

Table 2 Species of Candida in Patients with Otomycosis

Species	Number (n=56)	Percentage
Aspergillus spp	32	53.1
Candida spp	24	42.9
Candida parapsilosis	10	10/24 (41.66)
Candida tropicalis	6	6/24 (25.00)
Candida krusei	3	3/24 (12.5)
Candida kefyr	2	2/24 (8.33)
Candida glabrata	1	1/24 (4.1)
Candida utilis	1	1/24 (4.1)
Candida albicans	1	1/24 (4.1)

Table 3 Antifungal Susceptibility Among Candida Strains

Species	Antifungal Agent	Percentage of Sensitivity
Candida spp.	Nyst 1.25 µg/mL	42
	Ampho 2 µg/mL	38
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	25
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	33
	Micon 2 µg/mL	29
	Itra 1 µg/mL	54
	Vori 2 µg/mL	96
	Fluco 64 µg/mL	79
Candida parapsilosis	Nyst 1.25 µg/mL	10
	Ampho 2 µg/mL	30
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	0
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	0
	Micon 2 µg/mL	0
	Itra 1 µg/mL	50
	Vori 2 µg/mL	90
	Fluco 64 µg/mL	90
Candida tropicalis	Nyst 1.25 µg/mL	67
	Ampho 2 µg/mL	17
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	33
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	33
	Micon 2 µg/mL	33
	Itra 1 µg/mL	33
	Vori 2 µg/mL	100
	Fluco 64 µg/mL	33
Candida krusei	Nyst 1.25 µg/mL	67
	Ampho 2 µg/mL	67
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	67

Table 3 (continued)

	Candida Strains	Percentage of Sensitivity
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	67
	Micon 2 µg/mL	67
	Itra 1 µg/mL	67
	Vori 2 µg/mL	100
	Fluco 64 µg/mL	100
Candida kefyr	Nyst 1.25 µg/mL	50
	Ampho 2 µg/mL	50
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	50
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	100
	Micon 2 µg/mL	50
	Itra 1 µg/mL	100
	Vori 2 µg/mL	100
	Fluco 64 µg/mL	100
Candida albicans	Nyst 1.25 µg/mL	100
	Ampho 2 µg/mL	100
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	0
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	100
	Micon 2 µg/mL	100
	Itra 1 µg/mL	100
	Vori 2 µg/mL	100
	Fluco 64 µg/mL	100
Candida glabrata	Nyst 1.25 µg/mL	100
	Ampho 2 µg/mL	100
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	100
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	100
	Micon 2 µg/mL	100
	Itra 1 µg/mL	100
	Vori 2 µg/mL	100
	Fluco 64 µg/mL	100

Table 3 Antifungal Susceptibility Among Candida Strains

Species	Antifungal Agent	Percentage of Sensitivity
Candida utilis	Nyst 1.25 µg/mL	0
	Ampho 2 µg/mL	0
	Flucy 16 µg/mL	100
	Econ 2 µg/mL	0
	Keto 0.5 µg/mL	100
	Clotri 1 µg/mL	0
	Micon 2 µg/mL	0
	Itra 1 µg/mL	0
	Vori 2 µg/mL	100
	Fluco 64 µg/mL	100

*Spp: Specieses; Nyst: Nystatine; Ampho: Ampotericine B; Flucy: Flucytosine; Econ: Econazole; Keto: Ketoconazole; Clotri: Clotrimazole; Micon: Miconazole; Itra: Itraconazole; Vori: Voriconazole; Fluco: Fluconazole

Table 3 lists the in vitro susceptibility profile of 24 *Candida spp.* Isolates against ten antifungal agents, respectively. In the context of this study, it has been observed that Candida spp. displays complete sensitivity to two antifungal agents, specifically Flucytosine and Ketoconazole. Ten strains of Candida parapsilosis demonstrated resistance to Econazole, Clotrimazole, and Miconazole, while displaying elevated sensitivity towards Ketoconazole and Flucytosine. Conversely, Candida tropicalis exhibited notable sensitivity to Ketoconazole, Flucytosine, and Voriconazole.

Discussion

Otomycosis is prevalent in regions with high heat and humidity levels. The current samples were collected in the city of Purwokerto in the province of Central Java, where the climate is typically warm and humid.

The incidence of otomycosis varies geographically and is primarily influenced by environmental conditions. This pathology may account for up to 25% of infectious otitis in some tropical and subtropical regions, where it can reach high prevalence rates.[9] All ages are susceptible, although we have observed a disproportionate number of cases in patients aged 26 to 30. Distribution by gender is meaningless. In contrast to other series, there

was a slight preponderance of men in ours (51.1%; 49.9%). Some authors report a higher rate of male involvement. Saki et al.[3] and Navaneethan et al.[10] said that females are more susceptible to otomycosis than males.

Otomycosis is typically a unilateral disease, with bilateral involvement being infrequent. Compared to the left side, the right side was more prevalent in our study (59.6% vs. 40.4%). Similar to the study by Aremu et al.[11] and Pandey et al.[12], bilateral involvement was observed in only 12.7 percent of cases. Most people are right-handed and tend to self-clean their right ear more frequently with unsterile objects.

Candida parapsilosis, Candida tropicalis, Candida krusei, Candida kefyr, Candida glabrata, Candida utilis, and *Candida albicans* were identified in this study. *Candida parapsilosis* was the most commonly observed species in *Candida spp.* Culture examination, followed by *Candida tropicalis*. *Candida albicans* were discovered in only one culture. Our findings are consistent with those of Kim[13], who discovered that *Candida parapsilosis* was most prevalent in *Candida spp.* cultures. In contrast, Otašević et al.[14] and Gharaghani et al.[15] discovered that *Candida albicans* were the most abundant Candida species in adult patients with otomycosis. The results of this study differ from those of a study conducted by Kiakojuri et al.[8], which found the highest prevalence of *Candida orthopsilosis* in cultures of *Candida spp*. Fungi causing otomycosis vary geographically. The prevalence of *Candida parapsilosis* in our region may be attributable to environmental factors or a strong preference of this species for colonizing the external auditory canal.[13]

The sensitivity of Candida spp. to Flucytosine and Ketoconazole was found to be 100 percent, with Voriconazole achieving a sensitivity of 96 percent. These results contrast with those reported by Kiakojuri et al., who observed good sensitivity of Candida spp. to Nystatin, Clotrimazole, and Fluconazole in otomycosis patients. Additionally, the current study's findings slightly differ from those of Otasevic et al., who reported excellent sensitivity of Candida parapsilosis to Amphotericin B, Itraconazole, and Voriconazole in an antifungal sensitivity test. In contrast, our study showed good sensitivity of Candida parapsilosis to Flucytosine, Ketoconazole, Voriconazole, and Fluconazole.

The arsenal used to treat Candida infections consists of a variety of chemical classes. The efficacy of azoles, polyenes, echinocandins, nucleoside analogs, and allylamines varies according to the type and site of infection as well as the sensitivity of the Candida species. The most popular class of antifungal medications used to treat and prevent Candida infections are azoles. An essential enzyme in the manufacture of ergosterol, 14alpha demethylase encoded by Erg11p gene, is the target of azoles. Azoles successfully reduce the cell's ergosterol levels by binding to Erg11p. Its inhibition is caused by the bond between the free nitrogen atom of the azole ring and the iron atom of the enzyme's heme group. The buildup and metabolism of 14alpha methylated sterol species result in the creation of hazardous chemicals that cannot effectively replace ergosterol. Aside from this, azoles are also accountable for raising the quantities of reactive oxygen species (ROS). The generation of poisonous sterols and elevated ROS levels both prevent the infected fungus from growing.[16,17,18]

Polyenes medicines are fungicidal and target ergosterol in the plasma membrane. They create pores when they bind to ergosterol. Monovalent ions (K+, Na+, H+, and Cl) quickly leak out of pores, which results in the death of fungus cells. Nystatin and amphotericin B are examples of polyene medicines.[17,18]

The incidence of fungal infections has increased dramatically during the past three decades, concurrently with growing acquired and intrinsic resistance to antifungal medications. Nevertheless, antifungal resistance must be evaluated independently for each antifungal class and fungus genus. Mechanisms of antifungal resistance to azole-class medicines can be caused by efflux mediated by multidrug transporters, decreased affinity in Erg11p due to mutations, overexpression of ERG11, and modifications in the ergosterol biosynthesis pathway. While the mechanism of resistance to polyene antifungal medicines is the absence of ergosterol (loss of function mutation in ERG3 or ERG6) and a decrease in ergosterol content in cells, ergosterol deficiency is the cause of polyene antifungal drug resistance.[18]

Candida albicans resistance to azole antifungals has been the subject of the most research. The existence of point mutations in ERG11 has been identified as a resistance mechanism in this species. Previous research has identified amino acid substitutions that decrease fluconazole susceptibility and noted that a number of these crucial allelic variations cluster in three "hotspot" regions within the Erg11p gene. The mechanism is identical to that of Candida parapsilosis; however, in Candida parapsilosis, there is a rise in the production of

major facilitator superfamily transporters, which reduces intracellular accumulation of azoles.[15]

Otomycosis is a common disease encountered in outpatient ENT care. Patients with superficial infections and chronic colonization should be treated with intensive debridement, cleansing, and topical antifungal medications. Systemic antifungal therapy should not be prescribed except for malignant invasive (acute or chronic) otitis externa complicated by mastoiditis, meningitis, or both. Most patients respond favorably to topical treatment. The benefits of topical antifungals include local application, rapid achievement of the desired drug concentration on the skin's surface after application, a higher antifungal engagement at the affected site, lack of systemic side effects and complications due to limited systemic absorption, and very low incidence of drug interaction.[19]

Ketoconazole, Flucytosine, and Voriconazole demonstrated excellent sensitivity in this study, but only Ketoconazole was listed in the National Formulary. It is available in both tablet and ointment form.[20] Because systemic treatment lengthens the drug route, is absorbed, and is distributed throughout the body, the effectiveness of therapy at the site of infection is diminished, making otomycosis challenging to treat and frustrating for both doctors and patients.[7,21] At the same time, ointments have the disadvantage of being unable to be applied in difficult-to-reach areas.[19] The limitations of the study including only using a single culture medium to detect fungal growth and no molecular analysis (e.g. DNA sequencing) to definitively confirm Candida species identification.

In conclusion, *Candida parapsilosis* is the most prevalent otomycotic Candida pathogen complex, accounting for 41.66% of the isolates. Based on the susceptibility test, it has been determined that the otomycosis agents found in our hospital are sensitive to Ketoconazole, Flucytosine, and Voriconazole.

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CASE REPORT

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Giant Pyonephrosis Due to Calculus of Ureter: A Case Report

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Abstract

Giant pyonephrosis (GP) is a rare and severe form of pyonephrosis characterized by a massive enlargement of the affected kidney due to the accumulation of infected fluid. This study presents case of a 51-year-old male patient with giant pyonephrosis who underwent nephrectomy as treatment. The clinical manifestations of giant pyonephrosis are nonspecific, necessitating the use of imaging and laboratory techniques to aid in diagnosis. Nephrectomy is the preferred treatment option for these patients. One week after nephrectomy, the laboratory results showed improvements. Making the right treatment decision is challenging in this particular case.

Keywords: Abdominal mass, case report, giant pyonephrosis, ureteropelvic junction obstruction

Introduction

Pyonephrosis is an uncommon medical condition characterized by the accumulation of pus within the kidney, resulting from an obstructed urinary tract. This condition is considered rare and occurs infrequently in the general population. Pyonephrosis typically arises as a complication of untreated or recurrent urinary tract infections, kidney stones, or structural abnormalities within the urinary system.[1] GP is a rare and severe form of pyonephrosis characterized by a massive enlargement of the affected kidney due to the accumulation of infected fluid.[2] The exact definition of the fluid volume in giant pyonephrosis is not found in the literature. However, giant hydronephrosis was initially described by Stirling in 1939 as the accumulation of more than 1000 mL of fluid in the excretory system of the kidney,[3] while through imaging, features of the hydronephrotic renal pelvis that meet or cross the midline, occupy the hemiabdomen, and extend along five or more vertebral lines.[4] The specific epidemiology of pyonephrosis has not been found thus far. However, according to a study by Boeri et al., women are more commonly affected by pyonephrosis (56.5%) compared to men (43.5%), with an average age of 58.5 years.[5] The resulting urinary stasis leads to bacterial colonization of the obstructed system, which subsequently causes rapid progression causing urosepsis and septic shock. The mortality rate associated with septic shock can reach up to 50%.[6] Treatment of GP relies on the kidney functional status and underlying etiology ranging from simple nephrostomy to nephrectomy.[2] Our patient with a unilateral GP underwent a right open nephrectomy through various considerations explained further. The purpose of this article is to present case reports of GP in adults and a review of the literature.

Case

A 51-year-old Javanese man came to the emergency department of Bhakti Asih Hospital with a chief complaint of rapid enlargement of the abdomen that started 2 weeks ago. Mild abdominal pain was also felt intermittently with gross hematuria. There were no complaints of either fatigue, fever, nausea, and vomiting. The patient also had no known prior surgery, kidney stone disease, hypertension, diabetes, or any other urological related diseases.

The patient's vital signs were stable (blood pressure 120/80 mmHg), respiratory rate of 16 respirations per minute, pulse rate of 83 beats per minute, and axillary temperature show

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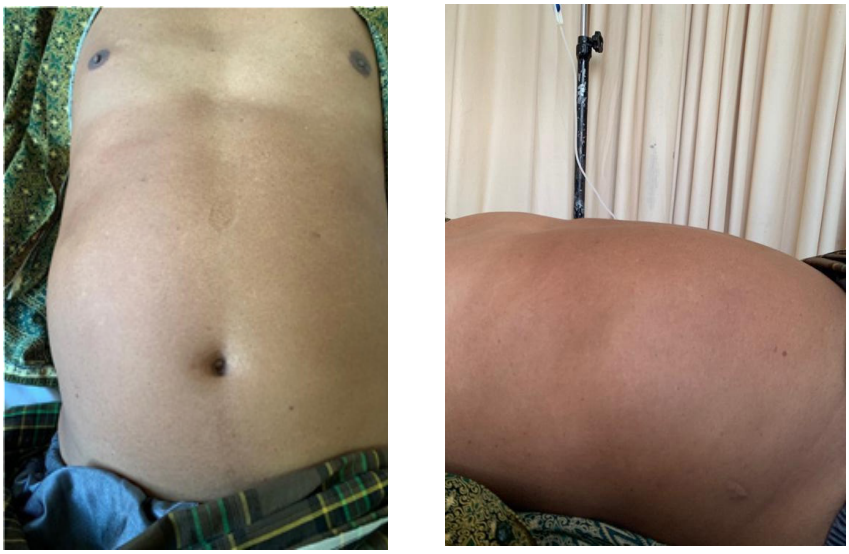

Figure 1 Clinical Picture. (A) Front view; (B) Lateral View of the Supine Position

36.2°C. The total body weight was 62 kg, Clinical examination showed abdominal distension, dullness to percussion, and a palpable mass with solid consistency with tenderness on the right side across the midline with right costovertebral tenderness (Figure 1).

Laboratory investigations were in normal range hemoglobin 11.3 g/dL (12.0–18.0 g/dL), erythrocytes 3.92 10^6/uL (4.0–55 10^6/uL), platelets 750,000/uL (150.000–450.000 /uL) urea 33.8 mg/dL (15–40 mg/dL), creatinine 1.13 mg/dL (0.7–1.4 mg/dL) aside from leukocytosis of 17,890 /uL (4.000–11.000 / uL). Chest X-ray examination revealed an elevation on the right diaphragm. A plain abdominal examination revealed multiple opaque lesions in the right kidney area, with the contour which appears enlarged. (Figure 2). Ultrasonographic examination showed grade 4 right hydronephrosis and hydroureter with a suspect of ureterolithiasis; Nephrolithiasis multiple mid and lower pole of the right kidney (with the biggest size of 2.03 cm) (Figure 3).

The treatment plan initially involved

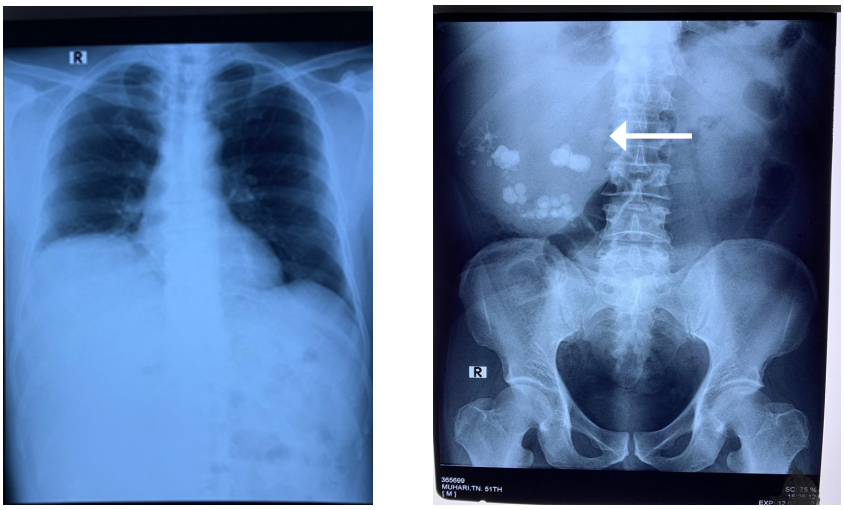

Figure 2 (Left) Chest X-ray; (Right) Plain Abdominal X-ray. (White arrow: Suggestive of a Semiopaque Stone in the Ureter)

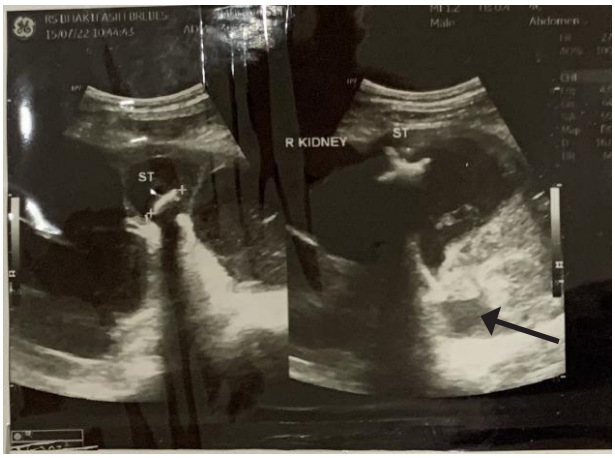

Figure 3 Abdominal Ultrasound. (Indicative of a Ureteral Stone Causing Obstruction)

performing a nephrolithotomy to remove the stones. However, during the operation, the presence of pus indicated a prolonged infection that had caused damage to the kidney. Meanwhile, the left kidney was functioning normally. As a result, a total nephrectomy was then carried out with a duration of 2 hours. A total of approximately 1500 mL of cloudy and seropurulent fluid was aspirated and drained, along with taking several stones from the right kidney, one of which was located at the ureteropelvic junction (UPJ) and at the proximal ureter (Figure 4). After nephrectomy, the size of the right kidney measures 24x20x18 cm. A drain was inserted into the abdominal cavity and the fascia and skin were closed. The patient was discharged with improvement on the 3rd postoperative day. Then, the patient was followed up 1 month later without any complaints and a routine blood tests and kidney function examination. The results of the routine blood tests showed Hb: 12 g/dL, leukocytes 8.000/uL, platelets 189.000 /uL, while the kidney function examination showed a slightly elevated urea of 38 mg/dL and creatinine 1.2 mg/dL.

Discussion

Pyonephrosis is a suppurative infection in the upper urinary tract and differs from infected hydronephrosis in the presence of pus.[2] This condition is commonly associated with parenchymal destruction of the kidney and a

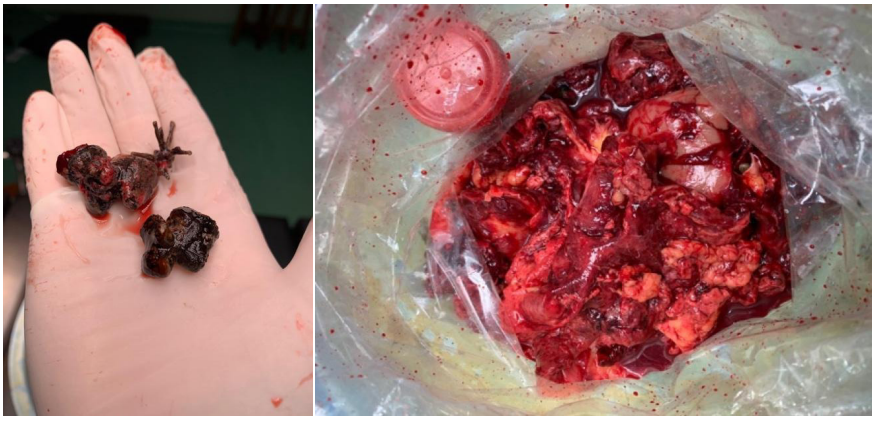

Figure 4 (Left) Kidney Stones Extracted During Nephrectomy; (Right) Macroscopic Specimen Shows Hydronephrosis of the Right Kidney

decline in kidney function.[7,8]

The main anatomical factor in pyonephrosis is ureteral obstruction. Stones are the most common cause, accounting for more than 70% of cases, as seen in this particular case.[5,7] The causes of obstruction can be categorized as intrinsic (stones, fungal balls, papillary necrosis, blood clots, UPJ obstruction, upper urinary tract malignancies) or extrinsic (bladder tumors, prostate cancer, retroperitoneal tumors or lymph nodes encroachment, compression by lower pole vessels). Intrinsic factors involve conditions that occur within the urinary tract itself, while extrinsic factors involve external structures or tumors compressing or obstructing the ureter. These obstructions disrupt the normal flow of urine, leading to urinary stasis, dilatation of the renal pelvis, and subsequent infection.[7]

Common clinical manifestations of pyonephrosis typically include flank pain, nausea, vomiting, fever, and general weakness.[7,9] Hematuria and abdominal masses are considered atypical presentations. Approximately 15% of patients may remain asymptomatic. In our case, a mass was identified in the midline of the right abdomen.[2]

The diagnosis of pyonephrosis is established based on clinical presentation, urine analysis, and radiological imaging.[2] Ultrasonography is known to be highly effective in diagnosing pyonephrosis, with a sensitivity of 90% and specificity of 97% in differentiating it from hydronephrosis.[10] Ultrasonographic findings indicative of pyonephrosis including the presence of hydronephrosis associated with signs of hyperechoic debris within the collecting system. These findings are fairly specific, as their absence rules out pyonephrosis with high accuracy.[10] CT scan is often performed in cases of pyonephrosis, with or without intravenous contrast administration, depending on kidney function. CT findings of pyonephrosis may reveal thickening of the renal pelvis wall (>2 mm), inflammatory changes in the parenchyma or perinephric area, dilation and obstruction of the collecting system, and the presence of gas-fluid or fluid levels within the intrarenal collecting system. It is often challenging to differentiate simple hydronephrosis from pyonephrosis based on fluid attenuation measurements, although recent studies suggest that patients with pyonephrosis may exhibit higher Hounsfield Unit (HU) values. [10] In this case the diagnosis was made based on clinical symptoms, abdominal x-ray, and abdominal ultrasonography. All considered differential diagnoses are abnormal ascites, intra-abdominal cysts, and adrenal cysts.[11,12]

The treatment options for pyonephrosis include nephrostomy, retrograde ureteral stents, pyeloplasty in cases of UPJ obstruction, and nephrectomy.[5,13,14] Antibiotic treatment has shown limited effectiveness in managing pyonephrosis, thus making surgical intervention necessary for proper management.[13] Percutaneous nephrostomy is the initial management for pyonephrosis, aiming to drain pus from the renal cavity. Another alternative is to perform a retrograde ureteral stent.[6] Nephrectomy is typically considered for patients with a non-functioning kidney, which often occurs in cases of long-standing pyonephrosis, while the contralateral kidney remains healthy.[2,7] In our case, nephrectomy was deemed necessary due to prolonged obstruction, resulting in non-functioning of the right kidney, while the contralateral kidney remained healthy.

Therefore, reducing the risk of kidney infection remains the best modality in a preventive measures including drinking a lot of fluids distinctly water, urinating when needed, and emptying the bladder after sexual intercourse may help preventing an upward bacteria infection from the urethra.[6]

This research did not incorporate computed tomography (CT) scans and urine cultures due to the unavailability of requisite hospital resources, thereby introducing potential hazards associated with anatomical variations during surgical interventions and the targeted administration of antibiotic treatments.

In conclusion, GP is a rare and life-threatening condition. Stone is a common cause. Obstruction results in urinary stasis, causing dilation of the renal pelvis and leading to infection. This can ultimately lead to sepsis and septic shock, which have the potential to be fatal. Prompt and accurate diagnosis is crucial for reducing mortality rates. Management options include percutaneous nephrostomy, retrograde ureteral stent placement, pyeloplasty for cases of UPJ obstruction, and nephrectomy. Nephrectomy is recommended when kidney function is impaired, and the infection persists to the point where it poses a life-threatening risk.

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Impact of Severe Preeclampsia on the Incidence of Low-Birth-Weight Babies

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Abstract

Infant birth weight is an important indicator of survival, growth potential, and developmental capacity. Maternal health plays an important role in determining the well-being of newborns. A complicated pregnancy, inclusive of conditions such as preeclampsia, elevates the risk of giving birth to a low birth weight (LBW) baby. This study aimed to compare the impact of severe preeclampsia on the incidence of LBW babies in Dr. Dradjat Prawiranegara General Hospital Serang, Indonesia. This case-control analysis included 148 parturients recruited randomly from June to October 2022. Logistic regression was used as the analytical tool, with P=0.000 considered as demonstrating a significant association. The incidence rates of LBW and severe preeclampsia in 2018 were 19.84% and 14.15%, respectively. The case group recorded LBW within the weight range of 1,000-2,450 g, with 38% of them were Small for Gestation Age (SGA), while 50% and 12% were Appropriate for Gestational Age (AGA), and Large for Gestational Age (LGA), respectively. In contrast, the control group, with birth weights ranging from 2,600-4,500 g, 13.50% were SGA, while 77% and 9.50% were AGA and LGA, respectively. Parity was a confounding factor influencing the incidence of LBW, while maternal age did not present a significant correlation. Pregnancies with severe preeclampsia were found to have a 29-fold increased likelihood of delivering LBW babies compared to the control group when controlling for parity (P=0.000, CI 95%). Hence, women with severe preeclampsia pregnancies have a higher risk for delivering LBW babies of 29 times higher than the control.

Keywords: Battaglia and Lubchencho, fetal growth restriction, low birth weight, severe preeclampsia, uteroplacental insufficiency

Introduction

Birth weight of babies is an important indicator in assessing the prospects of survival as well as the potential for growth and developmental capacity.[1] The World Health Organization (WHO) has defined low birth weight (LBW) as birth weight <2,500 g regardless of gestation age since 1976. This classification has been refined to show very low (VLBW) ranging from 1,000 to 1,499 g and extremely low (ELBW) birth weight less than 1,000 g at birth. [2] LBW can be an effect of preterm (<37 weeks gestation age) or dysmature due to fetal growth restriction, or both.[2, 3] Based on gestational age, Battaglia and Lubchencho divided BW into three subgroups of babies. These include, large, appropriate, and small for gestational age, (LGA): babies >90th percentile, gestational age (AGA): babies between 90th and 10th percentile, and gestational age (SGA): babies <10th percentile. [4]

In 2015, 20,5 million (UR 17.4–24.0 million) live births were LBW, while 91% were from low-and-middle-income countries, mainly southern Asia (48%) and sub-Saharan Africa (24%).[5] Factors influencing LBW include maternal age (specifically <16/18 years of age or >40 years)[5-8] and parity.[7, 8] Preeclampsia is a predominant factor predictor for LBW and can affect perinatal survival.[3, 9]

Preeclampsia is a specific disease during pregnancy and commonly occurs after 20 weeks of gestation age.[10, 11] This condition significantly contributes to fetal-related complications associated with prematurity,[10] including acute or chronic placental insufficiency leading to fetal growth restriction, fetal distress, intrauterine fetal death (IUFD), and increased mortality rates.[12] The limited interventions available for the management and prevention of fetal complications associated with preeclampsia

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contribute to its responsibility for approximately 20% to 30% of all preterm births. The pathogenesis is intricate, including dysfunctional placentation, oxidative stress, and systemic inflammation. This leads to chronic ischemia of the placenta and reduced uteroplacental perfusion to the fetus, impacting fetal growth restriction and gestational age.[12]

LBW is a significant global public health concern, with over 80% of neonatal deaths attributed to newborns, comprising two-thirds preterm and one-third term SGA babies. An elevated risk of morbidity, stunting, hindered long-term development, lower IQ, and compromised physical health was also experienced.[5] The health of mothers is an important role in determining the well-being of babies.[3] Therefore, this study aimed to analyzed and discussed the magnitude of severe preeclampsia's impact on LBW. Furthermore, it investigated the impact of severe preeclampsia on LBW based on Battaglia and Lubchencho's curve.

Methods

This case-control study compared the impact of severe preeclampsia in both case-control groups. The study was conducted in RSDP Serang, Banten, Indonesia from June to October 2022.

The populations were all parturients that registered in the register book's patients in RSDP (2018). Inclusion criteria for eligible participants in the cases group were parturients with gestational age ≥24 weeks, babies' birth weight <2,500 g, singleton fetuses, and all types of labor spontaneously or terminated pregnancy. Inclusion criteria for eligible participants in the control group were parturients with gestational age ≥24 weeks, babies' birth weight ≥2,500 g, singleton fetus, and all types of labor spontaneously or terminated pregnancy. Exclusion criteria were <24 weeks gestational age, multiple fetuses, and maternal pregnancy complications, such as Diabetes Mellitus (DM), chronic lung disease, renal, and heart disease.

This study is a retrospective case control, sample size determination was calculated on the formulation for the case control based on the Lemeshow. Data collection techniques were carried out from secondary data, namely by analyzing the patient's medical record according to the criteria. The instrument used in this study was the checklist and each group consisted of a sample size of n=74, resulting in a total of 148 selected through a random process. The collected data were analyzed descriptively and analytically. Descriptive calculation presents statistical measures, namely amounts and percentages for categorical data, while analytic uses a Logistic Regression statistical test with risk factors. This study has received approval from the Ethical Committee of Polytechnic of the Health Ministry of Health of the Republik of Indonesia Tanjungkarang, Bandar Lampung, Indonesia, No. 018/KEPK-TJK/X/2022.

Results

The incidence rate of LBW in RSDP in 2018 was 19.84% and severe preeclampsia rate was 14.15%. In the cases group, LBW ranged from an average of 1,000 to 2,450 g, comprising 38% SGA, 50% AGA, and 12% LGA. In contrast, the control group showed birth weights ranging from 2,600 to 4,500 g, with 13.50% classified as SGA, 77% AGA, and 9.50% LGA.

Table 1 showed that maternal age was not confounding to the incidence of LBW, while parity was confounding to LBW due to OR change in the primary variable exceeding 10%.

Table 2 showed that pregnant women who experienced severe preeclampsia had 29 times greater chances of delivering LBW babies than pregnant women who did not experience severe preeclampsia after being controlled by the parity variable.

According to Table 3, characteristics of subjects in the case group found that advanced maternal ages ≥35 years lower than <35 years

Table 1 Confounding Test's Result for Age and Parity Category Regarding the Incidence of LBW for Maternity Women in Dr. Dradjat Prawiranegara Hospital Serang 2018

Variable	OR* Main Variable	OR Changes	OR Change Magnitude	Information
Severe Preeclampsia	28.129	-	-	-
Age category	Excluded	29.283	4.10 %	Not Confounding
Parity category	Excluded	17.912	36.32 %	Not Confounding

*OR=Odds Ratio

Table 2 Final Model Test Result Impact of Severe Preeclampsia on The Incidence of LBW on Maternity Women in Dr. Dradjat Prawiranegara Hospital Serang 2018

Variable	B	p-value	OR	95% CI	
				Lower	Upper
Severe Preeclampsia	3.377	0.000	29.283	11.204	76.539
Parity category	2.665	0.000	14.364	4.012	51.421
Constant	-10.072	0.000	0.000		

Table 3 Distribution of Subjects by Age, Parity, Gestational Age, Birth Weight, and The Birthweight Classification Based on Battaglia & Lubchencho on Case Group

	Maternal Age (Years)		Parity		Gestation Age (Week)		Birth Weight (Gram)		Battaglia & Lubchencho Birth Weight Classification		
	≥35	<35	P≥3	P<3	<37	≥37	<2,500	≥2,500	LBW SGA	LBW AGA	LBW LGA
Amount	35	39	45	29	45	29	74	0	28	37	9
Total (%)	47	53	61	39	61	39	100	0	38	50	12

(47% vs. 53%); parity ≥3 higher than parity <3 (61% vs. 39%); gestation ages <37 weeks greater than ≥37 weeks (61% vs. 39%); birth weights <2,500 g (100 %) (LBW); LBW in case group with LBW SGA 38%, LBW AGA 50%, LBW LGA 12%.

From Table 4, characteristics of subjects in the control group found that advanced maternal ages ≥35 years lower than <35 years (20% vs. 80%); parity ≥3 lower than parity <3 (27% vs. 73%); gestation ages <37 weeks lower than ≥ 37 weeks (2.70% vs. 97.30%); birth weights ≥2,500 g (100%); BW in control group with BW SGA 13.50%, BW AGA 77%, and BW LGA 9.50%.

Discussion

In this study, the incidence of LBW in RSDP was 19.84%. Simultaneously, the incidence of severe preeclampsia in RSDP in 2018 was reported as 14.15%. Regarding the fetal and maternal conditions, the management included either expectant or termination of pregnancy (TOP) and the only definitive treatment was delivery. However, the decision on whether to delay or proceed with immediate delivery is dependent on various factors, including gestational age, the severity of maternal complications, and the well-being of the fetus.[13] In France, when severe preeclampsia cases arise between 24 to 26 weeks of gestational age, the decision between TOP and expectant management is subject to discussion, particularly when maternal disease severity is a concern, specifically when linked to fetal growth restriction. Conversely, in cases of severe preeclampsia occurring before 24 weeks of gestation age, patients receive counseling favoring TOP due to the increased risk of maternal complications and reduced perinatal survival. TOP is legally authorized and can be performed at any gestational stage when there is a potential risk leading to a life-threatening condition for the maternal or unborn baby, particularly when facing an incurable severe complication.[13, 14] The fetal complications' frequency differs related to the onset of preeclampsia. Early onset is related to significantly higher rates of adverse outcomes

Table 4 Distribution of Subjects by Age, Parity, Gestational Age, Birth Weight, and the Birthweight Classification Based on Battaglia & Lubchencho on the Control Group

	Maternal Age (Years)		Parity		Gestation Age (Week)		Birth Weight (Gram)		Battaglia & Lubchencho Birth Weight Classification		
	≥35	<35	P≥3	P<3	<37	≥37	<2,500	≥2,500	SGA	AGA	LGA
Amount	15	59	20	54	2	72	0	74	10	57	7
Total (%)	20	80	27	73	2.70	97.30	0	100	13.50	77	9.50

for the fetus, including fetal growth restriction and death.[12] This study only divided maternal age and parity into two categories due to knowing the risk factors or odd ratio (OR).

Table 1 showed that maternal age was not confounding to the incidence of LBW, while parity was confounding to LBW due to OR change in the primary variable exceeding 10%.

Based on gestational age, the definition of the term delivery differs in Battaglia and Lubchencho's curve. The term has been referred to 38 to 41 weeks gestational age by considering two two-week possibility errors in the estimation.[4]

Table 2 showed that pregnant women who experienced severe preeclampsia had 29 times greater chances of delivering LBW babies than those who did not experience severe preeclampsia after being controlled by the parity variable; p=0.000 (CI 95%). This study found complications related to severe preeclampsia in fetuses, such as growth restriction. [12]

In this study, maternal age only compares between those <35 years old vs ≥35 years old. Based on the result, maternal age was not confounding to the incidence of LBW, while parity was confounding to LBW. Different results were reported between this study with another in Ethiopia on the effects of maternal age and parity on birth weight of newborns among single and term deliveries. The result showed that women ≥40 years were associated with a higher risk of delivering LBW newborns with an AOR of 1.96 (95% CI=1.22, 3.20) vs. women 30–34 years.[8]

Despite a separate study on the impact of maternal age and parity on birth weight of newborns among mothers with singleton pregnancies and term deliveries in Ethiopia,[8] this study found that maternal age was not a confounding factor for LBW. This is consistent with the previous cross-sectional study on changing birth weight trends with maternal age in the Xi'an City of Northwestern China. The relationships between maternal age and birth weight, risk of LBW, and risk of macrosomia were reported to be non-linear. Specifically, birth weight showed an increase of 16.204 g per year for individuals under 24 years old (95% CI: 14.323, 18.086), followed by a decrease of 0.824 g per year in those aged 24–34 years (95% CI: -3.112, 1.464). The risk of LBW decreased with increasing maternal age until 36 years old (OR=0.917, 95% CI: 0.903, 0.932 for maternal age <27 years; OR=0.965, 95% CI: 0.955, 0.976 for maternal age 27-36 years), but increased for maternal age ≥36 years (OR=1.133, 95% CI: 1.026, 1.250). Conversely, the risk of macrosomia increased with maternal age (OR=1.102, 95% CI: 1.075, 1.129 for maternal age <24 years; OR=1.065, 95% CI: 1.060, 1.071 for maternal age 24-33 years; OR=1.029, 95% CI: 1.012, 1.046 for maternal age ≥33 years). For women aged 20–40 years, the threshold for maternal age associated with LBW was 36 years old, and the risk of macrosomia increased with advancing maternal age.[15]

Based on the final model test, the parity in this study is confounding to LBW and the present result only compares parity <3 and ≥3). This found the same results between this study with another in Ethiopia on the effects of maternal age and parity on birth weight of newborns among mothers with single and mature deliveries. Grand multiparous (parity ≥5) had an AOR of 3.89 (95% CI=2.19, 6.93) vs. multiparous (p=2–4). Nulliparous (p=0) had an AOR of 0.23 (95%CI=0.19, 0.38) vs. multiparous. The primiparous (p=1) had an AOR of 0.22 (95% CI=0.16, 0.30) vs multiparous. The grand multiparous had a higher risk of LBW vs. multiparous. The primiparous and nulliparous had less risk of delivering LBW babies vs. multiparous.[8]

Birth weight of babies in LBW category within severe preeclampsia case group averaged between 1,000 and 2,450 g. The distribution among SGA, AGA, and LGA LBW babies was 38%, 50%, and 12%, respectively. In contrast, the control group showed an average birth weight ranging from 2,600 to 4,500 g. The corresponding proportions for SGA, AGA, and LGA birth weight were 13.50%, 77%, and 9.50%, as shown in Tables 3 and 4.

Severe preeclampsia, defined as a condition with systolic ≥160 mmHg or diastolic ≥110 mmHg, commonly occurs after 20 weeks gestation, or is complicated by the evidence of maternal organ or uteroplacental dysfunction, including liver or renal dysfunction, pulmonary edema, thrombocytopenia, and central nervous system disturbances.[11, 12]

The results are rooted in the pathophysiological complexity of preeclampsia, a condition that remains inadequately comprehended. Preeclampsia includes abnormal placentation, systemic inflammation, and oxidative stress. The failure of appropriate remodeling of spiral arteries contributes to dysfunctional placentation, resistance in placental blood circulation, and hypo-perfusion of the placenta. This induces chronic placental ischemia,

leading to a reduction in blood circulation to the developing fetus. Therefore, these events lead to fetal hypoxia and give rise to adverse outcomes, including preterm birth, fetal growth restriction, fetal distress, and stillbirth.[12]

Based on a health profiles study from three districts/cities in East Java, Indonesia, pregnant women who suffered from preeclampsia were found to have LBW. These women will have physiological problems such as placental and uterine alteration due to decreased vascular circulation. Placental that does not function normally can cause fetal malnutrition, increasing the risk of delivering LBW babies.[3]

The limitations of the study were confined to the investigation of maternal age and parity, with an omission of consideration for additional factors such as maternal weight gain, BMI, and nutritional status, due to incomplete data. Moreover, the absence of crucial data supporting information on maternal health status shows the necessity for its completion, enhancing maternal enhancement and facilitating subsequent study endeavors. In conclusion, pregnancies with severe preeclampsia had more risk of delivering LBW babies 29 times larger than the control.

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Non-Metallic and Metallic Toxicant Exposures from Personal Care Products in Indonesian Male and Female Medical Students

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Abstract

Students can gain various benefits from their daily personal care products. However, the chemicals contained in these products may have adverse health effects. Regardless the inspection performed by regulatory agencies on these products, the products circulating in the market may still contain toxicants thus may jeopardize their safety for use. This study evaluated toxicant ingredients contained in personal care products used by male and female college students. This study was conducted from September to December 2022 on 23 male and 46 female college students of the Faculty of Medicine, Universitas Andalas, Indonesia. Data were collected using a 69-items validated questionnaire. Results were then presented as a distribution of products used categorized by body areas and potentially toxic metallic and non-metallic ingredients identified from their labels. Female college students used at least 10 personal care products, with a median of 19 products. Male students used at least four products and a median of eight products. Investigation on the label of skin, hair, eye, dental and oral, lips, and nail personal care products demonstrated the presence of metallic and non-metallic toxicants. Five metallic toxicants (aluminum, titanium, zinc, copper, and chromium) and 15 non-metallic toxicants (triclosan, talc, fragrance, parabens, butylated hydroxyanisole, butylated hydroxytoluene, diethanolamine, triethanolamine, butylene glycol, propylene glycol, polyethylene glycol, phthalates, benzophenone-3, acetone, and fluoride) were identified. Thus, numerous toxicants are present in marketed personal care products, and females are exposed more than males to these toxicants. Consumers need to be more critical in their choice of personal care products.

Keywords: Cosmetics, chromium, fluoride, survey and questionnaires, triclosan

Introduction

Personal care products are essential for college students for their inherent properties in cleaning, beautifying, increasing attractiveness, or changing appearance when applied to the skin, hair, lips, nails, teeth, and mouth.[1] Personal care products include shampoo, body soap, conditioner, cosmetics, toothpaste, mouthwash, lotion, cream, hair oil, hair tonic, hair dye, deodorant or antiperspirant, body scrub, sunscreen, nail polish, nail hardener, nail polish remover, etc.[2–4] Research on female students in South Carolina, United States, concluded that they use at least one personal care product, with an average of eight products daily.[2]

Consumers often only focus on product benefits and ignore the details of the ingredients listed on the packaging of personal care products, even though it is not uncommon for personal care products to contain endocrine-disrupting chemicals (EDCs) such as phthalates,

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parabens, triclosan, benzophenone-3 (BP-3), bisphenols, etc., which can interfere with the average production, secretion and transportation of hormones throughout the body.[2] The development of personal care product industry has increased in recent years. Manufacturers often add chemicals to increase the effectiveness of a product's function by adding chemicals. Most consumers consider these products safe, but an estimated 10% of the 10,500 chemicals in personal care products have yet to be evaluated for safety.[4] In personal care products circulating in the market, both those that have been or have not been recognized by the Indonesian regulatory agency on drugs and food safety (*Badan Pengawas Obat dan Makanan* (BPOM)), still contain non-metallic toxicants (hydroquinone, fragrance, phthalates, parabens, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), diethanolamine (DEA), triethanolamine (TEA), polyethylene glycol (PEG), propylene glycol (PG), butylene glycol (BG), benzophenone-3 (BP-3), oxybenzone, triclosan, acetone, poly- and perfluoroalkyl substances (PFAS), fluoride, and talc/talcum powder) and metallic toxicants (aluminum (Al), cadmium (Cd), lead (Pb), titanium (Ti), chromium (Cr), zinc (Zn), and copper (Cu)).[5]

Toxicants in personal care products indirectly have a tangible impact on the body and the surrounding environment. A previous study in the United States (US) showed that oxybenzone in sunscreen is not as effective against ultraviolet-A (UVA) exposure as avobenzone, titanium dioxide, or zinc oxide, even though these chemicals are associated with Hirschsprung's disease.[6] A 2021 Turkish study, which examined the aluminum metal found in personal care products, showed that aluminum is not related to breast tumors, but aluminum does increase the risk of developing Alzheimer's disease.[7]

Several previous studies, in general, examined the female sex who used personal care products more often.[2–4] This study aimed to compare the potential for exposure to the male and female sexes because the need for body care products is very important for male and female students. However, only a few students are aware of the dangers of the chemicals contained, and some are highly toxic.[4] Students of the medical education study program at the Faculty of Medicine, Universitas Andalas, especially senior-year students who have studied general toxicology and dermatology courses, must be more aware and concerned about the potential for toxic exposure from various sources. Therefore, it is interesting to assess the potential for senior students' exposure to toxicants from personal care products.

Methods

This study consecutively recruited 69 senior-year medical students (23 males and 46 females) at the Faculty of Medicine Universitas Andalas, Padang, West Sumatera, Indonesia. The minimal number of subjects was obtained by employing the Lemeshow formula. All subjects had taken dermatology and general toxicology courses, which may serve as background knowledge in choosing personal care products.

Personal care products in this study were products that are used to clean, prevent, treat, protect, beautify, increase attractiveness, change appearance, and for fragrance used by the students. To collect information on the types of personal care products used by the medical students within the last six months, in this study used a modified and translated

Table 1 Personal Care Products Used Based on Areas by Medical Students by Sex in the Last Six Months

Areas	Number of Products					
	Male			Female		
	Min	Max	Median	Min	Max	Median
Skin	2	10	6	5	20	11
Hair	1	3	1	1	6	3.5
Dental and oral	1	2	1	1	2	1
Lip	0	1	0	1	5	2
Nail	0	0	0	0	2	0
All areas	4	14	8	10	32	19

questionnaire from The Sister Study (https://sisterstudy.niehs.nih.gov/english/images/docs/PersonalCare-v3-508.pdf).[8] The questionnaire consisted of 69 items and was translated into Indonesian language before validated by content expert panels consisting of a pharmaco-toxicologist, a dermatologist, and a public health toxicologist. The reliability test of the questionnaire showed Cronbach's alpha value of 0.923. After obtaining approval from the institutional review board (No.951/UN.16.2/KEP-FK/2022), the study questionnaire was distributed online via a Google form (bit.ly/QuestionnairePCP) from September to December 2022.

All respondents opted to consent at the start of the questionnaire before responding to the questions regarding personal care product usage. Responses were collected and processed by classifying personal care products based on brands and variants. Each product's composition was recorded based on the product's ingredients label. Toxic ingredients were identified and classified as non-metallic and metallic toxicants. Toxicants were identified based on available scientific evidence of their unfavorable effects on animal and human health. Data were counted and presented as descriptive statistics and percentages (using MS Excel®) according to sex and frequency of the toxicant product.

Results

Personal care products often contain toxicants that may interfere with users' health in various ways over the short or long term. Excessive use of personal care products will increase a person's potential for exposure to toxic substances. Recently, the use of personal care products is

Table 2 Types of Toxicants in Skin Care Products Used by Medical Students

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Body soap (n=49)	Fragrance	49	100	Ti	10	20.4
	BHT	16	32.7	Zn	2	4.1
	PEG	14	28.6			
	PG	9	18.4			
	Paraben	8	16.3			
	BG	5	10.2			
	Talc	2	4.1			
	DEA	2	4.1			
	TEA	1	2			
	Triclosan	1	2			
	BP-3	1	2			
Perfume/ cologne (n=55)	Fragrance	54	98.2			
	PEG	17	30.9			
	BHT	10	18.2			
	PG	10	18.2			
Deodorant/antiperspirant (n= 37)	Fragrance	33	89.2	Al	33	89.2
	BHT	9	24.3	Ti	1	2.7
	PEG	9	24.3	Zn	1	2.7
	PG	8	21.6			
	BG	6	16.2			
	Paraben	4	10.8			
	Triclosan	4	10.8			
	Talc	1	2.7			

Table 2 (continued)

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Sunscreen (n=33)	Talc	32	97	Ti	9	27.3
	Fragrance	20	60.6	Zn	6	18.2
	PEG	18	54.5	Al	4	12.1
	BG	18	54.5			
	PG	14	42.4			
	BHT	9	27.3			
	TEA	8	24.2			
	Paraben	6	18.2			
	BP-3	1	3			
Lotion (n=42)	Fragrance	38	90.5	Ti	13	31
	Paraben	22	52.4	Al	7	16.7
	BHT	14	33.3	Zn	1	2.4
	TEA	12	28.6			
	PEG	12	28.6			
	PG	9	21.4			
	Talc	1	2.4			
Body scrub (n=24)	Fragrance	22	91.7	Ti	9	37.5
	PEG	16	66.7	Al	4	16.7
	PG	9	37.5			
	Paraben	8	33.3			
	BHT	7	29.2			
	TEA	7	29.2			
	BG	2	8.3			
	BP-3	2	8.3			
Skin whitening (n=4)	Fragrance	4	100	Ti	4	100
	BHT	2	50			
	Triclosan	1	25			
	Paraben	1	25			
	PG	1	25			
Body/foot/hand cream (n=7)	Fragrance	4	57.1	Al	1	14.3
	PG	3	42.9	Ti	1	14.3
	Paraben	2	28.6			
	BHT	1	14.3			
	TEA	1	14.3			
	PEG	1	14.3			
	BG	1	14.3			
Face wash (n=44)	Fragrance	34	77.6	Zn	4	9.1
	PEG	26	59.1	Ti	2	4.5
	BG	26	59.1	Al	1	2.3

Table 2 (continued)

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Face wash (n=44)	PG	18	40.9			
	Paraben	6	13.6			
	BHT	5	11.4			
	TEA	4	9.1			
	BP-3	1	2.3			
Face moisturizer (n=32)	BG	23	71.9	Cu	4	12.5
	PG	13	40.6	Ti	3	9.4
	Fragrance	12	37.5	Zn	3	9.4
	PEG	12	37.5	Al	1	3.1
	Paraben	7	21.9			
	TEA	5	15.6			
	BHA	1	3.1			
	BHT	1	3.1			
Face/makeup cleansing (n=17)	PEG	11	64.7	Zn	1	5.9
	Fragrance	10	58.8	Cu	1	5.9
	PG	8	47.1			
	Paraben	4	23.5			
	BHT	3	17.6			
	BG	3	17.6			
	TEA	1	5.9			
Face serum (n=28)	BG	18	64.3	Zn	3	10.7
	Fragrance	9	32.1			
	PEG	7	25			
	PG	7	25			
	BHT	5	17.9			
	TEA	3	10.7			
	BHA	1	3.6			
	Paraben	1	3.6			
Face cream (n=5)	Fragrance	5	100	Ti	3	60
	PEG	4	80	Al	1	20
	PG	2	40			
	BG	2	40			
	Paraben	2	40			
	BHT	2	40			
	BHA	1	20			
	TEA	1	20			
	Talc	1	20			

Table 2 (continued)

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Face powder (n=21)	Talc	17	81	Ti	10	47.6
	Fragrance	15	71.4	Zn	10	47.6
	BHT	5	23.8	Al	8	38.1
	Paraben	3	14.3			
	PEG	2	9.5			
	PG	2	9.5			
	TEA	1	4.8			
Blush on (n=13)	Talc	6	46.2	Al	5	38.5
	Fragrance	4	30.8	Ti	4	30.8
	Paraben	3	23.1	Zn	2	15.4
	BHT	3	23.1			
	BG	3	23.1			
	PEG	2	15.4			
	PG	2	15.4			
Foundation makeup (n=9)	PEG	7	77.8	Ti	8	88.9
	BG	3	33.3	Al	7	77.8
	Fragrance	2	22.2	Zn	3	33.3
	Talc	2	22.2			
	BHT	2	22.2			
	PG	1	11.1			
	Paraben	1	11.1			
Face toner (n=9)	BG	6	66.7			
	PG	5	55.6			
	PEG	4	44.4			
	Fragrance	3	33.3			
	Paraben	1	11.1			
	TEA	1	11.1			
Face mask (n=7)	BG	5	71.4	Al	2	28.6
	Fragrance	3	42.9	Ti	1	14.3
	PEG	2	28.6	Zn	1	14.3
	PG	1	14.3			
	Talc	1	14.3			
	Paraben	1	14.3			
Cushion (n=5)	PEG	5	100	Al	5	100
	BHT	3	60	Ti	5	100
	BG	3	60	Zn	2	40
	Fragrance	2	40			
	PG	1	20			

Table 2 (continued)

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Concealer (n=4)	BG	4	100	Al	3	75
	PEG	3	75	Ti	2	50
	BHT	2	50	Zn	2	50
	PG	1	25			
	Fragrance	1	25			
	Paraben	1	25			
Eyeliner (n=11)	PEG	8	72.7			
	PG	6	54.5			
	BG	5	45.5			
	Fragrance	1	9.1			
Eye shadow (n=6)	Talc	4	66.7	Zn	2	33.3
	Paraben	2	33.3	Al	1	16.7
	Fragrance	1	16.7	Ti	1	16.7
				Cu	1	16.7
				Cr	1	16.7
Eye serum (n=3)	Fragrance	1	33.3			
	TEA	1	33.3			
	PEG	2	66.7			
	BG	3	100			
Eye cream (n=2)	Fragrance	1	50			
	PEG	1	50			
	BG	1	50			

not only used by females but also by males. Table 1 presents the number of personal care products by area of use and the total number of benefits based on the male and female users in the last six months. The results showed that female students used at least ten personal care products, while male products used at least two in various regions in the previous six months.

Non-metallic and metallic ingredients have various functions in personal care products, but some have been shown to exert toxic effects. Table 2 describes the types of toxicants found on personal care products, classified based on the skin area application by the respondents. The result showed that in skin care products, body soap had the highest number of toxicants (11 non-metallic and two metallic toxicants), while eye cream had the lowest ones (three non-metallic toxicants). The non-metallic toxicants identified in personal care products included fragrance, BHA, BHT, PEG, PG, parabens, BG, talc, DEA, TEA, triclosan, and BP-3, while the metal toxicants identified were Zn, Al, Ti, Cu, and Cr.

Hair care products are other sources of potential toxicant exposure. Table 3 presents information on the types of toxic ingredients found in the hair care products used by the respondents. Mascara products were discovered to have the highest number of toxicants (eight non-metallic and three metallic toxicants), and hair vitamins had a single toxicant in its ingredients. The non-metallic toxicants identified were triclosan, PEG, BG, PG, talc, BHT, parabens, fragrance, DEA, and TEA, while the metal toxicants were Ti, Cr, Al, Cu, and Zn.

Dental and oral care products have the potential to be ingested by the nature of their use. Therefore, it is necessary to review the chemicals in dental and oral care products. Table 4 lists the toxic ingredients in the respondents'

Table 3 Types of Toxicants in Hair Care Products Used by Medical Students

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Shampoo (n=42)	Fragrance	42	100	Zn	14	33.3
	PEG	17	40.5	Ti	13	31
	PG	11	26.2			
	BG	3	7.1			
	Paraben	2	4.8			
	TEA	2	4.8			
	DEA	1	2.4			
Conditioner (n=20)	Fragrance	18	90	Zn	4	20
	PG	9	45	Cu	2	10
	PEG	4	20			
	BG	1	5			
	BHT	1	5			
	Paraben	1	5			
Hair oil (n=9)	Fragrance	7	77.8			
	PEG	3	33.3			
	PG	2	22.2			
	TEA	1	11.1			
	BHT	1	11.1			
	Paraben	1	11.1			
Hair tonic (n=9)	Fragrance	9	100	Zn	2	22.2
	PEG	8	88.9	Cu	1	11.1
	PG	6	66.7			
	BG	4	44.4			
	Paraben	2	22.2			
	Triclosan	1	11.1			
Hair vitamin (n=3)	Fragrance	3	100			
Hair perfume (n=2)	Fragrance	2	100	Zn	2	100
	Paraben	2	100			
	PEG	2	100			
	PG	2	100			
Hair mask (n=5)	Fragrance	4	80			
	PEG	3	60			
	PG	3	60			
	BG	2	40			
	Paraben	2	40			
	BHT	1	20			
	DEA	1	20			
	TEA	1	20			

Table 3(continued)

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Hair dye (n=5)	Fragrance	5	100	Ti	4	80
	PG	5	100			
Mascara (n=13)	PEG	6	46.2	Ti	5	38.5
	BG	5	38.5	Cr	3	23.1
	PG	4	30.8	Al	2	15.4
	Talc	4	30.8			
	BHT	4	30.8			
	Paraben	3	23.1			
	Fragrance	3	23.1			
	TEA	2	15.4			
Eyelash serum (n=1)	PG	1	100	Zn	1	100
	BG	1	100			

dental and oral care products. The respondents used mouthwash (with two identified non-metallic toxicants) and toothpaste (four identified non-metallic and three metallic toxicants). The non-metallic toxicants found in these products were PEG, PG, fluoride, parabens, and triclosan. Meanwhile, the metallic toxicants were Zn, Ti, and Al. This study found fluoride in the forms of sodium fluoride and sodium monofluorophosphate.

Lip care products are straightforward to reach the digestive tract, and therefore consumers need to be aware of the safety of ingredients contained in the products. Table 5 shows the types of toxicants in classified lip care products respondents use. Lip tint was found to have the highest number of toxicants identified, and lip serum products had the least number of toxicants. Toxicants in lip care products were found in non-metallic forms such as fragrance, talc, phthalates, BG, PEG, BHT, TEA, parabens, and PG. On the other hand, metal toxicants in lip care products were Al, Ti, and Zn.

Nail care products can flake or chip away and easily enter the oral cavity when users eat with their hands. Table 6 describes the toxicants identified in nail care products used by respondents. It was found that nail polish remover was the most frequent product with toxicants identified. The non-metallic toxicants identified were fragrance, PG, BHT, and acetone. Meanwhile, the only metal toxicant was Ti in nail care products.

Discussion

This study finds that female students typically use personal care products. The main reason for women using personal care products is

Table 4 Types of Toxicants in Dental and Oral Care Products Used by Medical Students

Product	Toxicant					
	Non-metallic	f	%	Non-metallic	f	%
Toothpaste (n=21)	PEG	10	47.6	Zn	6	28.6
	PG	6	28.6	Ti	5	23.8
	Fluoride	21	100	Al	2	9.5
	Paraben	2	9.5			
Mouthwash (n=7)	PG	3	42.9	Zn	2	28.6
	Fluoride	3	42.9			

Table 5 Types of Toxicants in Lip Care Products Used by Medical Students

Product	Toxicant					
	Non-metallic	f	%	Logam	f	%
Lip balm (n=17)	BHT	11	64.7	Ti	4	23.5
	Fragrance	10	58.8	Zn	2	11.8
	Paraben	4	23.5	Al	1	5.9
	PG	3	17.6			
	BG	2	11.8			
Lip tint (n=23)	*Fragrance*	15	65.2	Ti	4	17.4
	BG	11	47.8	Al	2	8.7
	PEG	8	34.8			
	BHT	5	21.7			
	TEA	4	17.4			
	Paraben	3	13			
	PG	3	13			
Lip cream (n=18)	*Fragrance*	17	94.4	Al	14	77.8
	Talc	7	38.9	Ti	6	33.3
	Paraben	3	16.7			
	PEG	2	11.1			
	PG	2	11.1			
	BG	2	11.1			
Lipstick (n=9)	*Fragrance*	7	77.8	Al	5	55.6
	Paraben	2	22.2	Ti	5	55.6
	BHT	2	22.2			
	Talc	1	11.1			
	Phthalate	1	11.1			
Lip gloss (n=6)	*Fragrance*	3	50	Al	2	33.3
	BHT	2	33.3	Ti	2	33.3
	PEG	1	16.7			
	PG	1	16.7			
Lip mask (n=2)	*Fragrance*	1	50	Al	1	50
	BHT	1	50	Ti	1	50
				Zn	1	50
Lip serum (n=3)	*Fragrance*	2	66.7	Al	1	33.3
	BHT	1	33.3			

explained by Dodson et al.[3] that women buy or use products because of their aroma and get recommendations from their environment or female friends. According to Hart et al.[2], women are culturally pressured to improve their beauty, hence using many personal care products. This fact puts women at a much bigger risk of exposure to toxicants in these products. Some toxicants may have a long half-life and circulate in the body for a long time, eventually carrying developmental risk to their offspring when the women conceive. Research on pregnant rats exposed to personal care products containing BP-3 showed disturbances in the growth of the rat fetus.[9]

The current study found triclosan as

Table 6 Types of Toxicants in Nail Care Products Used by Medical Students

Product	Toxicant					
	Non-metallic	f	%	Metallic	f	%
Nails polish (n=6)	PG	2	33.3	Ti	1	16.7
Nail polish remover (n=4)	*Fragrance*	4	100			
	PG	1	25			
	Aseton	1	25			
Nail moisturizer (n=1)	*Fragrance*	1	100			
	BHT	1	100			

an ingredient in body soap, deodorant or antiperspirant, skin whitening, and hair tonic. Triclosan is added for its anti-bacterial and anti-fungal property. Triclosan disrupts endocrine and cardiovascular function, affects the immune response, and increases reactive oxygen species production.[10] The US Food and Drug Administration (FDA) has banned several triclosan soap products. However, the Indonesian BPOM only limits its content levels in personal care products (a maximum content of 0.3% in products other than mouthwash, 0.2% for mouthwash).[11]

Among non-metallic toxicants, talc was found in numerous products (body soap, deodorant or antiperspirant, sunscreen, lotion, foundation, face powder, blush on, eye shadow, face cream, face mask, mascara, lip cream, and lipstick). Talc is added to products to soften or smoothen the skin and reduce friction by absorbing moisture, clot prevention agents, and skin protectants. Acute toxicity of talc can manifest as dry or erosion of the skin in an experiment on rabbits. In chronic toxicity, talc can induce endobronchitis or narrowing of the airways in someone exposed to large amounts of talc in the facial area.[12]

Other non-metallic toxicants in this study, such as parabens, phthalates, and UV filters (benzophenone-3), may act as EDC. Parabens are preservative compounds in personal care products. Several studies have shown a link between parabens and the occurrence of breast, ovarian, and testicular cancer in humans.[13] Ingested, inhaled, or applied onto the skin, and phthalates can particularly affect the nervous system.[14] Research on pregnant mice exposed to BP-3 on the skin of mice with a dose similar to sunscreen resulted in stunted fetal growth. [9]

Acetone is a toxicant found in nail polish remover. Acetone can be absorbed through the digestive tract, lungs, and skin, affecting the central nervous system, digestive, respiratory, cardiovascular, and endocrine systems.[15] Fluoride is found in dental and oral care products to prevent dental caries. Mouthwashes containing fluoride are not generally recommended for children under 6 or 7 years of age because most children cannot yet spit effectively. It has a potency of 90% being ingested daily. Fluoride that enters the intestine will be absorbed quickly. Ingested fluoride, approximately 55% will be stored by children and 36% by adults; the rest of the absorbed fluoride will be excreted as urine. Children retain or keep higher levels of ingested fluoride than adults because of the large surface area provided by the growing mass of bone crystallites. Fluoride can cause systemic effects on the respiratory, cardiovascular, gastrointestinal, hematologic, hepatic, renal, and muscular or bone systems.[16]

Exposure to personal care products containing fragrances in substantial concentrations can trigger asthma-like symptoms.[17] Fragrance interaction with the olfactory receptors may induce physiological markers of stress, by enhancing the cortisol and cardiovascular stress response.[18] In addition, fragrance compounds with estrogenic properties (phthalates and parabens) can play an active role in breast cancer.[17] BHA and BHT are toxicants in personal care products. Although BHA and BHT are chemically similar, the mechanism of toxicity is different between the two. BHA toxicity can cause apoptosis because it can increase caspase-3 activity, while BHT shows a decrease in caspase-3, accompanied by an increase in dead cells.[19]

Diethanolamine, in personal care products, functions as a pH adjuster. DEA toxicity can cause ulceration, irritation, and crusting. It can even lead to ulcerative necrosis to the lower part of the dermis, which has been tested on experimental animals.[20] Triethanolamine functions as a surfactant and pH regulator in

skin cosmetics and hair conditioner. However, TEA may cause skin irritation and, if ingested, can affect the kidneys, liver, erythrocytes, and nervous system.[21] This toxicant is found in almost all personal care products. For its function, PEG has the role of a surfactant, emulsifier, cleansing agent, humectant, and skin conditioner.[22] PEG exposure leads to toxicity mainly via the oral route. PEG's target organ is generally the kidney. If PEG enters the systemic circulation, acidosis is expected due to PEG acid metabolites.[23] Propylene glycol is a solvent used in personal care products as a skin conditioning agent, viscosity-reducing agent, solvent, and one of the ingredients for fragrance in cosmetic products. However, prolonged and high dose exposure can cause toxicity. Propylene glycol is not irritating to the skin but has the potential to induce an inflammatory response when mixed with methylisothiazolinone. Methylisothiazolinone is a heterocyclic organic compound that has long been used in personal care products.[24] Butylene glycol has characteristics as a solvent and viscous liquid and has antimicrobial properties. However, in a study in Japan, there were cases of increased allergies due to BG.[25]

In this study, several metallic toxicants were identified in personal care products used by our respondents. The most frequently found metal toxicant was Ti. Titanium in the form of nanoparticles has the potential to be inhaled and accumulate in the lungs. Besides that, it can be spread throughout the body through the lung barrier.[26] Another toxicant is Al. Aluminum is a buffering agent, corrosion inhibitor, pH regulator, and agent to prevent accumulation. Aluminum can also treat hyperhidrosis, therefore often used in deodorant/antiperspirant products. However, it is thought that the frequent use of Al-containing antiperspirants may play a role in cases of breast cysts because cases of breast cysts often occur on the outer upper part of the breast adjacent to the axilla, by obstructing secretory ducts. [7] Another metallic toxicant is Zn, which has UV protective, anti-acne, anti-inflammatory, anti-bacterial, and anti-odour properties. However, Zn in the form of ZnO compounds has toxic properties because it can enter the blood-brain barrier, which may lead to neurotoxicity and affects brain physiology.[27]

Copper is another toxic metal found in this study. Copper correlates with headaches, migraines, mental depression, and even autism due to Cu accumulation in the hair.[28] Chromium is a metal toxicant that is used as a coloring agent. Chromium is one of the most common allergens found in cosmetics.[5]

The USFDA last updated the lax regulation regarding ingredients in personal care products in 1938, despite the proven detrimental effects of EDC exposure from personal care products.[29] Similarly, in Indonesia, BPOM, as a regulatory body, has not banned related ingredients that are proven to be harmful, only limiting the concentration of ingredients in these products.[11] Consumers need to build awareness of the potential toxic effect of various ingredients in personal care products on chronic exposure. Combined exposure to multiple toxicants may further complicate the long-term safety of personal care products. There should be advocacy to protect consumer safety and to push the industry to provide safer alternatives.

This study has limitations inherent to the survey method used to collect the data, which accuracy relied heavily on the respondents. The identification of potential toxicants relied solely on the written ingredients on the products' label. The list of products in the questionnaire might not be exhaustive, therefore any other products used by the respondents were possibly unaccounted for.

It is concluded that numerous non-metallic and metallic toxicants in personal care products are used by college students, where females are exposed more than male users. As an implication of this study, it is recommended that while waiting for regulatory bodies to amend industry practices that favor consumer safety, consumers need to be more critical in choosing personal care products.

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RESEARCH ARTICLE

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Use of sEMG for Swallowing Muscles Activity Quantification in Acute Phase of Stroke

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Abstract

Early diagnosis of dysphagia and aspiration risk is very important in minimizing the risk of various medical consequences. This study aimed to establish a scientific database for future sEMG-based dysphagia screening investigations by examining the electrical activity of swallowing muscles in acute stroke cases. A quantitative cross-sectional study was conducted on 61 stroke inpatients admitted to Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, from July to November 2019. The objective of this study was to quantify electrical activities of the suprahyoid (SH) and infrahyoid (IH) muscles during swallowing. Patients participated in both dry swallowing and a 3 mL water swallowing task, with the sEMG used to measure electrical activity parameters (duration, swallowing initiation, time-to-peak, and amplitude) on both paretic and normal sides. The Wilcoxon test was used to compare the electrical activity parameters between the patients paretic and normal sides. Only amplitude showed a significant difference between the paretic and normal side ($p=0.023$) when performing the 3 mL water swallowing test. Other parameters did not exhibit significant differences in activity between muscle groups during both swallowing tests ($p>0.05$), although varying water volumes led to distinct activities in both muscles. Despite the absence of a clear pattern in SH and IH contractions during swallowing, the result showed that the sEMG quantification method might become a promising method for screening dysphagia, complementary to FEES and VFSS. The non-invasive and cost-effective sEMG method can serve as an early screening tool for dysphagia in stroke patients. This study underscores the importance of further investigation on sEMG use, incorporating a larger sample size and diverse cohort results with various swallowing exercises (varying in volume and viscosity) to validate the use of sEMG in dysphagia screening.

Keywords: Deglutition, electromyography, stroke

Introduction

Stroke is a neurological deficit that can cause many functional disturbances, including swallowing disorders (dysphagia), which affects 44–63% of acute stroke cases. However, most cases of dysphagia in this stage of stroke are rarely found with simple clinical examinations.[1] This condition can significantly diminish post-stroke patients quality of life, leading to increased morbidities such as pneumonia, malnutrition, dehydration, and mortality.[2] Early identification of dysphagia and aspiration risk is crucial as it can reduce the incidence of various medical complications, such as aspiration-related medical complications, prevent long-term hospitalization, reduce medical costs in general, and precision of rehabilitation plans, particularly for stroke patients.[3]

Early screening for dysphagia is crucial, typically initiated with non-instrumental tests. If the screening shows suspicion of dysphagia, a more comprehensive test using instruments will be carried out. This instrumental screening test can directly evaluate the impaired swallowing mechanism, significantly improving the accuracy of the diagnosis of swallowing disorder. Despite its diagnostic benefits, challenges persist in conducting instrumental screening tests on acute stroke patients.[3]

The elaborate process of swallowing engages over 50 head and neck muscles, with crucial

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roles played by muscles like the suprahyoid and infrahyoid. Weakness and coordination disorder of these muscles post-stroke can cause aspiration during swallowing.[3] This abnormality can be detected through surface electromyography (sEMG). This device has been proven safe, and it can measure the capability of swallowing muscles in healthy and dysphagic populations.[4]

sEMG is relatively affordable, non-invasive, and sensitive enough for dysphagia screening. It provides a semi-quantitative measurement of dysphagia caused by pharyngeal muscle dysfunction.[5] Subsequently, sEMG measurement of the muscles engaged in swallowing has been used to assess swallowing capability in sub-acute stroke. Patients with infarct stroke, as observed through sEMG, exhibited delayed onset, longer pre-trigger duration, and shorter electrical swallowing muscle activity than healthy people, which describes an impaired larynx protection mechanism.[6]

There is a scarcity of studies conducting instrumental dysphagia screening in acute stroke patients. However, in Italy, Giannantoni et al. used sEMG in the acute stroke population in 2016 and described decreased pharyngeal muscle motility.[5] The suprahyoid (SH) and infrahyoid (IH) muscles have been widely studied among the muscles included in swallowing. The positioning of the hyoid is the mutual function of SH and IH muscle contraction. The SH muscles can lift the hyoid bone in anterosuperior motions, which elevate the floor of the mouth to facilitate deglutition. The suprahyoid (SH) muscles play a role in depressing the jaw and aiding in a broad opening of the mouth, while the infrahyoid (IH) muscles stabilize the hyoid bone. The IH muscles depress the hyolaryngeal complex, and the thyrohyoid muscle, one of the four IH muscles, moves the larynx anterior-superiorly during swallowing. Moreover, the SH and IH muscles help the upper esophageal sphincter (UES) open by elevating the hyoid bone.[6]

Many studies using sEMG have primarily focused on evaluating swallowing only by measuring SH muscle activity in healthy patients or those already experiencing swallowing problems. Only a limited number of studies have included stroke patients and measured the activity of infrahyoid IH muscles. Therefore, this study aimed to quantitatively describe the electrical activities of SH and IH muscles in acute stroke patients to provide a scientific database for future investigation on dysphagia screening using sEMG.

Methods

A cross-sectional, analytic descriptive, observational study of the electrical signals of SH and IH muscles during swallowing was carried out in 61 patients with acute-phase stroke who were selected by consecutive sampling and obtained informed consent. Subsequently, this study was carried out in the neurological ward of Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia, from July to November 2019 after obtaining approval from the ethics committee (LB.02.01/X.6.5/62/2019).

Patients were included if diagnosed with the acute phase (day 1–2 weeks after onset) hemiparesis due to the first stroke or a recurrent stroke that occurred on the same side (proven by CT scan), aged 18-69 years old, and consented to participate. Patients were excluded if they showed an inability to follow simple instructions, were hemodynamically unstable, or still had impaired consciousness after two weeks following the stroke onset, had a history of trauma or surgery in the head or neck region, exhibited Parkinson's symptoms, had a pacemaker, or taken muscle-relaxing drugs in two weeks before the measurement.

The variables collected were the characteristics of the patients and sEMG parameters, including duration, swallowing onset, time-to-peak, and amplitude. A neurologist initially evaluated the patients stroke using the NIHSS score. Subsequently, patients were divided into three groups based on the severity of their strokes: mild stroke, defined as an NIHSS score of 8 or less; moderate stroke, defined as an NIHSS score of 9 to 15; and severe stroke, defined as an NIHSS score of 16 or more. sEMG data were obtained from SH and IH muscles in dry swallowing and 3-ml-water swallowing tests. In this study, sEMG (myoscan sEMG T9503M)

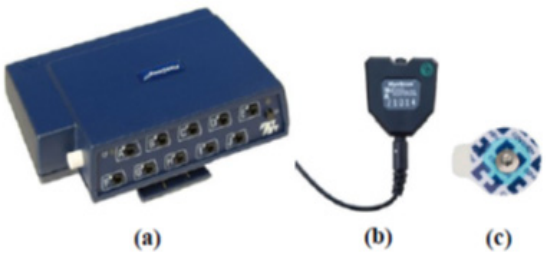

Figure 1 (a) Instrument Flex Comp Infiniti, (b) EMG sensor Myoscan, (c) Disposable EMG Electrodes

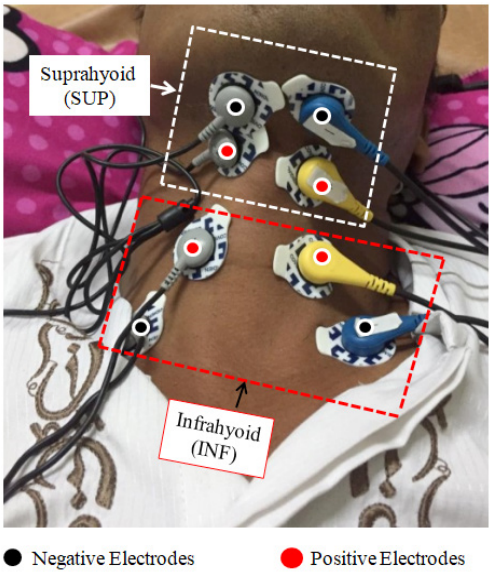

Figure 2 Illustration of the Placement of sEMG Electrodes[7]

was used in recording the measurements while connected to a bio-amplifier (FlexComp System with BioGraph Infiniti Software version 6.1.4 developed and manufactured by Thought Technology Ltd, Montreal, Canada) that has ten measurement canals with high sampling speed (2048 sample/second) and 14-bit resolution (data range 0-16383) (Figure 1).

This device has an internal calibration scheme which was activated to ensure the signal was in high resolution. The triangular head sensor on sEMG represents the two bipolar active electrodes (positive and negative) and one reference electrode (ground). The sensors specifications are as follows: a pre-amplifier that can detect a potential difference of 0–2000 μV accurate to ±5% and ±0.3iV; a high input impedance value (1,000,000 MΩ); a sensitivity of ≥0.1 iVRMS; CMRR at 50-60Hz:-180dB; and CMRR at 10-1000 Hz: -130dB. Disposable EMG Ag/AgCl electrodes were then attached to the skin on the area between the two innervation zones and reference points (Figure 2).

The EMG signals obtained from FlexComp, representing the four muscle groups included in swallowing, were processed using BioGraph Infiniti before being recorded on a computer, and the problem of study guided the data analysis process. The Sapiro-Wilk test was applied to verify the normality of the data first, statistical analysis was in line with the study objectives and hypotheses. Finally, the Wilcoxon test was used to compare the electrical activity parameters between the patients paretic and normal sides because the data were not normally distributed. The p-value is the commonly used significance value; if $p \leq 0.05$, the data is considered significant. All data were then processed using the SPSS 17.0 version for Windows (Figure 3).

Results

As shown in Table 1, the majority of patients were male (51%), aged 60-69 years (21%), with

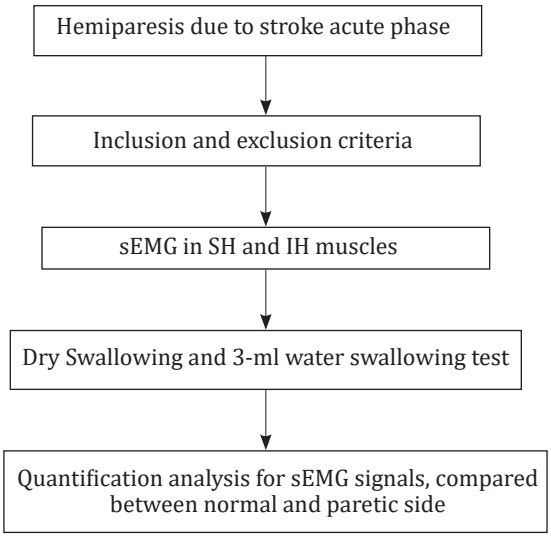

Figure 3 Research Flow

Table 1 Characteristics of Subjects

Variable	(n=61)	%
Gender		
Male	31	51
Female	30	49
Age (years)		
20–29	2	3
30–39	4	7
40–49	17	28
50–59	25	41
60–69	13	21
Site of Lesion		
Cortical	11	18
Subcortical	40	66
Cortical, Subcortical	10	16
Level severity of the stroke (NIHSS score)		
Mild	25	41
Moderate	36	59

NIHSS: National Institutes of Health Stroke Scale

subcortical lesions (66%) and moderate severity of stroke (59%). In two swallowing tests, the data were not normally distributed, and there were no significantly different patterns in electrical activity parameters between the paretic compared to the normal side except in amplitude when performing dry swallowing and 3-mL water swallowing tests, where paretic side have higher amplitude compared to normal side (Table 2).

Discussion

The SH and IH muscles contribute to hyoid bone stability, generating a neutral resultant force through their contractions. Motoric deficit caused by stroke is frequently followed by skeletal muscle flaccidity. Reduced suprahyoid tension due to flaccidity prompts an increase in infrahyoid tension, maintaining a neutral resultant force.[8] A previous study found that in dysphagia, there was a delayed onset of SH in the starting pharyngeal phase followed by delayed laryngeal excursion.[9]

An impartial quantitative assessment of stroke patients prone to dysphagia is crucial. Among various methods used for evaluating dysphagia, the gold standard for diagnosing and formulating a plan for proper care and its treatment is the fiberoptic endoscopic evaluation of swallowing (FEES) and the videofluoroscopic swallowing study (VFSS), subjectivity remains due to qualitative assessments by doctors. In addition, the VFSS has limitations, such as its high cost, radiation impact, and the need for special equipment and skilled operators.[10]

The active participation of specific muscles in swallowing has been studied by surface electromyography (sEMG). Electrodes on the skin capture the motor unit action potentials generated by muscle contraction. Due to the sequential activation of motor units and an increase in the firing rate of all motor units recruited, sEMG signal's amplitude, which can be graphically represented, increases with an elevated muscular contraction force.[11] sEMG signal can be used to study dysphagia as it serves as an effective indicator of essential mechanical events in swallowing. Consequently, it can be employed to screen for swallowing disorders, including oropharyngeal dysphagia post-stroke.[12]

In sEMG examination, swallowing onset represents the initial contraction of muscles during the swallowing activity. The onset parameter shows the sequence of muscle contractions, showing which muscle group contracts earlier and which experiences delayed contraction during swallowing. This study found that the onset of SH and IH was not significantly different on the paretic side compared to the normal side in dry-swallowing and the 3-mL water test. However, when the volume is increased, the onset tends to be earlier (Table 2). This is in line with the result of the earlier study that bolus volume significantly affects pharyngeal pressure and swallowing timing.[13]

Duration is a parameter used in evaluating the length of the muscle contraction period when swallowing. The tendency of prolonged duration in SH and IH in stroke patients compared to those that are healthy may show a slow reaction in the swallowing process, specifically during the pharyngeal phase. In this study, the duration of SH and IH contractions was not statistically different between the paretic and the normal side when performing a dry and 3-ml-water test (Table 2). The duration of both groups muscle contractions in the dry swallowing test showed a shorter duration than 3-ml-water swallowing, which discovered that the amount of water swallowed affects how long swallowing muscles contract.[14]

Table 2 Electrical Activity Parameters of Suprahyoid and Infrahyoid Muscles in Dry Swallowing and 3-mL Swallowing Test

Electrical Activity Parameters			Suprahyoid				Infrahyoid			
	Median Minimum		Median	Min.	Max.	p-value	Median	Min.	Max.	p-value
Dry swallowing	Onset (seconds)	paretic side	0.17	0.01	1.14	0.483	0.05	0.01	1.16	0.328
		normal side	0.17	0.01	1.01		0.06	0.01	3.53	
	Duration (seconds)	paretic side	2.51	1.08	4.51	0.900	2.79	0.55	4.56	0.906
		normal side	2.59	0.71	4.55		2.76	0.00	4.59	
	Time-to-Peak (seconds)	paretic side	1.23	0.33	3.50	0.318	1.20	0.45	3.40	0.399
		normal side	1.23	0.39	2.91		1.29	0.33	3.53	
	Amplitude (mV)	paretic side	20.78	4.08	69.98	0.201	13.98	3.95	51.02	0.301
		normal side	20.73	0.13	393.51		14.43	3.83	53.11	
3-ml-water swallowing	Onset (seconds)	paretic side	0.04	0.01	1.08	0.710	0.04	0.01	0.94	0.495
		normal side	0.07	0.01	1.18		0.06	0.01	0.93	
	Duration (seconds)	paretic side	2.83	0.89	3.74	0.163	2.83	0.99	3.99	0.390
		normal side	2.79	0.55	3.84		2.83	0.99	3.98	
	Time-to-Peak (seconds)	paretic side	1.16	0.35	3.25	0.991	1.22	0.44	3.15	0.186
		normal side	1.22	0.19	2.91		1.33	0.35	3.08	
	Amplitude (mV)	paretic side	22.33	4.51	64.08	**0.023***	13.35	5.54	64.84	0.407
		normal side	20.81	0.12	82.52		14.69	3.64	92.67	

*Significant (p≤0.05); max: maximum; min.:minimum

Time-to-peak is needed for muscle to reach maximal contraction in one swallowing action. This parameter refers to the duration between the onset and the amplitude of the electric signal. In both swallowing tests, this study showed that the time-to-peak for both SH and IH muscles was not significantly different. Subsequently, the same was true with another result in the time parameter variables, showing that the bolus volume was included in the result. The result showed that if the volume increases, the paretic side reaches maximal contraction faster than the normal side.

The time parameters of the electrical signal, which include duration, onset, and time-to-peak, used in sEMG study for swallowing evaluation have lower reliability than the amplitude parameter.[4,15] Studies using time parameters have yielded varied results, influenced by factors such as the limited number of electrodes used for muscle examination and the characteristics of the patients included. This prevents a complete picture of the sequential activity of all the muscles included in swallowing.

Aging can induce physiological changes, potentially affecting swallowing timing. Showing age-related alterations in timing measures has proven challenging, but the literature suggests

a correlation with diminished tongue muscular strength. Timing is crucial because a safe and effective swallow depends on careful timing and coordinated contraction of several muscles in the oropharynx. Although it was already clear that older individuals' swallowing mechanisms differed from those of younger adults and the elderly, studies found that many swallow timing characteristics seemed unaffected by aging.[16] The majority of participants in this study were 50 to 59, which may have influenced the result, although the cut-off age for older patients was 60, the characteristics could have affected the results.

Apart from aging, the investigation into potential gender differences in the typical physiological swallowing process has gained recent attention. However, this area requires further study to draw conclusive results. An earlier study showed a gender difference in the length of the cricopharyngeal opening for a 10 mL bolus, with the opening persisting longer in women. Age-related disparities in hyolaryngeal excursion between men and women were likely connected. The proposal suggested that women retained more muscle reserve than men. In addition, it has been observed that variations in the pharyngeal phase of swallowing are due to anatomical differences between men and women, in which the pharynx is more extended in men than women. However, this conclusion is still subject to debate, as a recent study suggested that age and gender did not significantly impact the oral transition of the bolus. Earlier studies showed that age and gender have a significant effect on the bolus's oropharyngeal transition and could vary depending on the bolus volume. In Table 1, data showed that the patients gender proportion was almost the same between men and women, minimizing potential influence on the results.[17]

Studies have indicated that crucial factors in determining the prognosis or severity of dysphagia include the location and severity of the initial stroke. Previous studies showed that dysphagia may be influenced by brainstem or posterior circulation abnormalities. However, in some studies, the site of the stroke was not associated with dysphagia, which means that the initial severity of the stroke was found to be the leading risk factor for dysphagia.[18] There is a need for further due to the discrepancies in the studies about the relationship between these parameters and sEMG in patients with dysphagia.

The oropharyngeal sensory receptors modulate the swallowing motor response, which controls the physiological swallowing reaction. A higher amplitude of the electrical signal of a contracting muscle is caused by an increased release rate of motor units or an increased number of recruited motor units.[19] As shown in Table 2, this study found the SH amplitude to be higher than the IH amplitude in both maneuvers. Physiologically, SH and IH muscle groups work together in elevating the larynx and hyoid bone. Previous investigations have shown that the IH muscles are engaged during the oropharyngeal motor response sequence after the SH muscle. Subsequently, IH having a lower amplitude than SH shows that SH muscle is more dominant in keeping the larynges elevated during swallowing.[19] In the dry swallowing test, the amplitude did not significantly differ between the paretic and the normal side. The amplitude was significantly different in the 3-mL water swallowing test. If the bolus is bigger, the amplitude increases, showing SH needs more effort to swallow in line with the higher bolus.

The swallowing function may be accurately and objectively estimated using sEMG. This procedure was reliable, non-invasive, radiation-free, affordable, effective, and easy to use. The widespread adoption of sEMG as a dysphagia screening method faces challenges due to the need for anatomical expertise, as accurate electrode placement in specific regions is crucial.[20] This study method uses four electrodes to record different muscle activities (suprahyoid and infrahyoid muscles) associated with swallowing to make it a simple and non-invasive tool to quantify muscle activity during swallowing.

An earlier study using the same sEMG procedure has successfully showed the evaluation of muscle activity in swallowing using quantification methods in the time domain. In comparison between healthy patients and post-stroke patients, the result showed that contraction duration and time to peak of maximum contraction in healthy patients were shorter than in stroke patients. This study found that the evaluation using the time domain method for swallowing analysis is promising and holds the potential to support dysphagia screening.[7] Further analysis in the time domain for the pattern of SH and IH contraction in the dysphagia sample showed no specific pattern, except for the amplitude, where some limitations may come into play.

This study used sEMG on suprahyoid and infrahyoid muscles to compare the muscle activity during swallowing and tried to explore all available parameters in detail. However, some

limitations need to be addressed in further studies. This study did not measure sensibility in oral, pharyngeal, and laryngeal areas that may influence motoric control when swallowing in stroke patients. The swallowing test only used a small volume of water, which may not give an accurate picture of muscle electrical activity during daily swallowing activity.

This study has limitations, as it exclusively used stroke patients without healthy control patients, preventing a comparison of electrical activity parameters between the two groups. Further studies with a control group that matches the age, gender, and other comorbidities should be carried out to minimize bias that may become confounding factors. Besides that, to evaluate anatomical active participation in the swallowing process, standard tools such as Flexible Endoscopic Evaluation of Swallowing (FEES) or videofluoroscopy are also needed as objective tools for dysphagia diagnosis.

In conclusion, quantifying SH and IH contractions in swallowing in the acute phase of stroke using sEMG resulted in varied outcomes with no specific pattern. This shows that, except for amplitude, the contraction of the SH and IH muscles on the paretic side did not differ significantly from the normal side. Despite the significant difference in amplitude, the results showed the potential use of sEMG in screening dysphagia during the early phase. The quantification through sEMG results showed that SH-dominated and varied volume boluses produced different results. Subsequently, future studies should use a larger sample in a cohort study, more diverse swallowing activities (different volume and viscosity), and a control group (healthy patient group) that matches the age, gender, and other comorbidities that may become confounding factors. This study serves as a preliminary analysis, and future study is essential to uncover additional parameters in muscle activity for screening dysphagia. Establishing a cut-off value for the electrical activity of swallowing muscles using sEMG in the early phase of dysphagia can be explored as a complementary procedure alongside FEES and VFSS.

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Validity Test For C-Reactive Protein and Ferritin Level in Moderate and Severe Covid-19 Patients

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Abstract

Mild, moderate, severe, and critical COVID-19 are associated with hyperinflammation. The CRP and ferritin are acute phase proteins that marks incidence of inflammation and used as the paramaters of hyperinflammation. This study aimed to determine the validity of CRP and ferritin level examination in moderate and severe COVID-19 since the time of admission. This was a cross-sectional analytical retrospective study with on moderate and severe COVID-19 patients admitted to Dr. Hasan Sadikin General Hospital Bandung, Indonesia, during the period of March 2020 to December 2020. The CRP and ferritin levels were obtained since the beginning of admission to the fourth day since admission on patients without any history of anemia. Subjects in this study were divided into moderate and severe COVID-19 groups based on the 3rd edition of COVID-19 Prevention and Control Guideline issued by the Ministry of Health Republic of Indonesia. Each group consisted of 30 subjects. The cut-off value was 7.65 mg/dL (AUC 0.698) for CRP and 963.1 mcg/L (AUC 0.938) for ferritin. The validity of ferritin vs CRP were reflected respectively as follows: 93.3% vs 76.7% sensitivity; 80.0% vs 63.3% specificity; 82.4% vs 67.6% PPV; and 92.3% vs 73.1% NPV. The validity of ferritin was proven to be superior as it significantly increases since day one, persisted longer and reaches its peak on the16th day. Meanwhile, CRP increases within 6-8 hours and reaches its peak within 48 hours after inflammation, then declines soon afterwards.

Keywords: COVID-19, CRP, ferritin, validity

Introduction

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) is a collective of clinical respiratory symptoms caused by coronavirus 2 genus β coronavirus which may also induce multi-organ disturbance and elicit clinical manifestation in various organs, including gastrointestinal, hepatic, cardiovascular and neural organs.[1] Based on World Health Organization (WHO) data in September 13th, 2021, the morbidity and mortality rate of Coronavirus Disease 2019 (COVID-19) cases reached 224,511,226 cases, especially on elderly patients with comorbidities, owing 4,627,540 cases.[2]

The incubation period for COVID-19 infection is around 5-6 days with various clinical symptoms, including mild symptoms, i.e., fever, anosmia, pharyngitis, cough, myalgia, cephalgia, gastrointestinal disturbance, to severe and critical degree symptoms, such as shortness of breath and sepsis which may end in death.[3]

The pathomechanism for appearance of various clinical symptoms in COVID-19, begins with innate and adaptive immune response, which will release pro-inflammatory cytokines, including TNF-α, IL-1, IL-6 and IL-8, also infection markers such as procalcitonin, CRP and ferritin. T-helper, T-suppressor and T-regulator cells are found reduced in COVID-19 patients, with T-helper and T-regulator cells significantly lower on severe cases.[4] There are various indicators to evaluate the severity and prognosis of COVID-19 based on the degree/clinical stage, which research is currently still ongoing.[5]

C-reactive protein is an acute phase protein synthesized by the liver as a response towards the increased IL-6 during systemic inflammation and severe infection, and is used as a marker to evaluate and monitor patients infected with SARS-CoV-2, especially those with severe cases.[6] On a study by Tan et al., showed that the increase of CRP is significant on the beginning of severe COVID-19 infection. C-reactive protein is also

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associated as prognostic marker on the initial phase of COVID-19 infection.[7,8] Based on a study by Huang et al., CRP level of ≥ 1 mg/dL is associated with poor COVID-19 clinical outcome and increased CRP is also associated with sepsis and mortality.[9]

Another marker, i.e., ferritin, is also an acute phase protein, which plays role as immune dysregulation mediator, and its incidence is associated with hyperferritinemia and cytokine storm as a result of overexpressed pro-inflammatory cytokine. Ferritin synthesis is mediated by interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF).5 High ferritin level on patients with severe and critical disease showed systemic inflammation associated with the severity degree of COVID-19. A study by Gandini et al., showed that the mean level of ferritin on mild, moderate, severe and critical COVID-19 are 281 µg/L, 308 µg/L, 741 µg/L and 1640 µg/L, respectively.10,11 Hence, examination of ferritin level during the beginning of the disease may identify the severity of the disease and the prognosis of patients infected with COVID-19.12

Considering that the increase of CRP and ferritin on COVID-19 patients during the initial phase of the disease may provide insight about the severity of the disease, the authors of this paper is intrigued to determine the validity of CRP and ferritin level for moderate and severe COVID-19 infection.

Methods

This was an analytic observational study which data were obtained via retrospective cross-sectional method. Data was obtained using Laboratory Information System (*Sistem Informasi Laboratorium*) and medical records in March 2020 to December 2020 during the peak of Delta variant in Dr. Hasan Sadikin General Hospital Bandung. The subjects of this study were all moderate and severe COVID-19 patients admitted in isolation ward at Dr. Hasan Sadikin General Hospital Bandung. The inclusion criteria for the subjects in this study was adult patients (aged ≥ 18 years), admitted in isolation ward, COVID-19 diagnosis confirmed within ≤ 48 hours since admission based on nasopharyngeal swab examination with real-time PCR, included in moderate and severe COVID-19 cases based on 3rd Edition COVID-19 Prevention and Control Guideline Ministry of Health Republic of Indonesia (Year 2020) (*Pedoman Pencegahan dan Pengendalian* COVID-19 *Kementerian Kesehatan RI edisi 3* (*Tahun* 2020)), which stated that severe disease was marked by respiratory rate of >30 times/minute and/or SpO_2 <93% and/or presence of sepsis signs or respiratory distress, moderate disease was categorized on patients with pneumonia clinical signs (fever, cough, dyspnea) without signs and symptoms of severe disease, and mild disease was accompanied with symptoms but without evidence of viral pneumonia or without hypoxia. The categorization was conducted during initial assessment in the hospital, while CRP and ferritin level was examined during the initial time of admission, or 4 days the latest after isolation admission. The exclusion criteria of subjects in this study were COVID-19 patients with anemia and patients with incomplete laboratory results medical record data. The evaluated laboratory criteria for moderate and severe COVID-19 were ferritin and CRP levels. COVID-19 patients were divided into 2 groups, namely, moderate and severe degree groups.

Statistical analysis was conducted using unpaired t-test if the data were normally distributed and using non-parametric test (Mann-Whitney U test) if the data were not normally distributed. Analysis of receiver operator characteristic (ROC) curve was conducted to obtain cut-off value and area under curve (AUC) value, afterwards, validity test for CRP and ferritin was conducted for moderate and severe cases, remarking sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV). The study data were documented in Microsoft Excel® table and were processed using SPSS® 19.0 software. This study has been approved by Medical Research Ethical Committee, Dr. Hasan Sadikin Hospital Bandung (No.: LB.02.01/X.6.5/188/2021).

Results

Laboratory data and medical records data during March 2020 to December 2020 yielded data of 106 patients. The study subject characteristics data were presented on Table 1 below.

Table 1 showed that there was a significant association among gender, comorbidity, patient condition at discharge with disease severity degree, CRP and ferritin level (p<0.05%), and that there was no significant difference between age and disease severity degree (p>0.05). Females dominated moderate degree disease, while on severe disease was dominated by males (83.3%). On age group, it was known that the

Table 1 Characteristics Data of Study Subjects based on Degree of Severity

Patient Characteristics	Degree		p-value
	Moderate n=30	Severe n=30	
Gender:			
Male	13 (43.3)	25 (83.3)	0.001[a]*
Female	17 (56.7)	5 (16.7)	
Age (years)			
Mean ± SD	50 ± 18	57 ± 12	0.107[b]
Comorbidities			
With comorbidities	11 (36.7)	20 (66.7)	**0.020[a]***
Without comorbidity	19 (63.3)	10 (33.3)	
Discharge condition			
Improved	30 (100.0)	19 (63.3)	<0.001[a]*
Died	0 (0.0)	11 (36.7)	
CRP (mg/dL)			
Median (Min-Max)	6.74 (0.07 – 26.34)	10.24 (0.43 – 38.62)	0.008[c]*
Ferritin (mcg/L)			
Median (Min-Max)	618.2 (33.7 – 1636.7)	1741.8 (738.6 – 6766.2)	<0.001[c]*

Note: Analysis using [a]Chi Square test, [b]Unpaired t-test, [c]Mann-Whitney test, *significant if p<0.05

mean age was on the fifth decade. Severe cases were dominated by patients with comorbidities (66.7%) and those who were discharged with improvements (100%) were dominated by severe degree disease. Data analysis showed that the median of CRP value was (10.2 mg/dL) and for ferritin was (1741.8 mcg/L) which were higher on severe COVID-19 cases.

The ROC curve of CRP towards severity degree of COVID-19 patients was presented in Figure 1, while the ROC curve of ferritin towards severity degree of COVID-19 patients was presented in Figure 2.

Table 2 showed that combined CRP and ferritin level has lower validity compared to CRP alone and ferritin alone. Ferritin has a higher validity with optimum cut-off value of 963.1 mcg/L (p=<0.001) with sensitivity of 93.3% and specificity of 80.0% in predicting the severity degree of COVID-19 patients at the beginning of admission.

Discussion

This study utilizes data of 60 COVID-19 patients, in which moderate degree cases were dominated by female, while on severe degree were dominated by male. This result was in accordance with the study result by Gandini et al., which showed that there were 54.3% female subjects and 45.7% male subjects on mild-moderate degree, while on

Table 2 Validity Test of CRP and Ferritin towards Severity Degree of COVID-19

Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP (mg/dL)				
7.65	76.7	63.3	67.6	73.1
Ferritin (mcg/L)				
963.1	93.3	80.0	82.4	92.3
CRP 7.65 mg/dL and Ferritin 963.1 mcg/L	73.3	70.0	71.0	72.4

Note: PPV: positive predictive value, NPV: negative predictive value

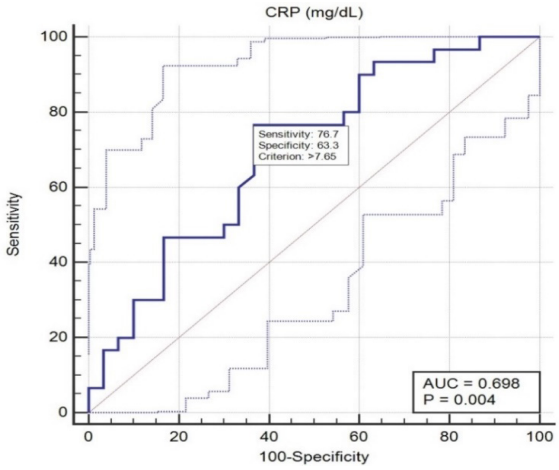

Figure 1 ROC Curve of CRP towards Severity Degree of COVID-19 Patients

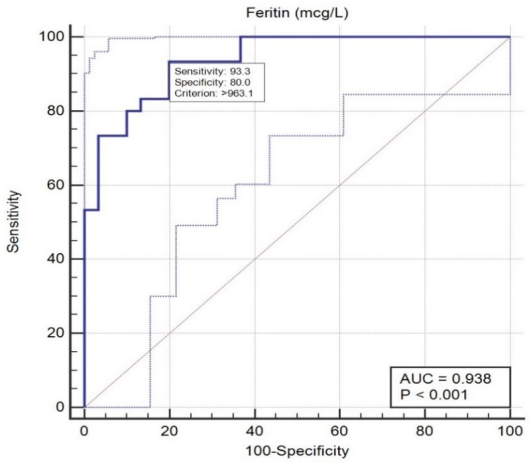

Figure 2 ROC Curve of Ferritin towards Severity Degree of COVID-19 Patients

the severe degree cases there were 26.7% female subjects and 73.35% male subjects. Because the X-chromosome encodes several genes associated with immune responses, women are likely to have lower inflammation responses than men. Moreover, men have higher susceptibility to infections because testosterone's role that inhibit immune processes.[13] Based on that study, the incidence of acute respiratory distress syndrome (ARDS) and systemic inflammation was associated with history of comorbidities such as cardiovascular disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, lung cancer on male subjects.[11] In this study, male subjects have comorbidities, which was mostly diabetes mellitus, hypertension and cardiovascular disease.

Characteristics data (Table 1) regarding age distribution showed that the mean age for moderate degree was from 56-65 years age group and for severe degree was from >65 years age group. This result was consistent with a study by Tural et al., which stated that the mean age of study subjects was from 62 years age group and with presence of comorbidities, namely cardiovascular disease, diabetes mellitus, hypertension. This study result showed that severe degree group has more comorbidities compared with moderate degree group. COVID-19 patients were mostly from the age group of >60 years and has poorer prognosis considering the declined immune system and specific immunoregulation in the elderly. Elderly patients had the tendency to develop multisystem organ dysfunction with age, and it has also been known that elderly patients had a decreased natural innate and adaptive immune system, causing a continuous production of inflammatory mediators and cytokines, known as chronic systemic inflammation which occurs physiologically with aging and might potentially induce cytokine storm.[14,15]

This study showed that there was still several complaints or symptoms at discharge on 36.7% subjects on severe degree group (Table 1), which was consistent with the study findings of Mahmud et al., stating that severe COVID-19 patients were still symptomatic at discharge probably associated with severity of the infection, length of stay, risk factor and history of comorbidities in the patient.[16]

This study showed that there was a difference of CRP and ferritin level between moderate and severe cases, in which the median CRP and ferritin on severe cases were higher than the moderate cases. This result was reciprocal with study result by Smilowitz et al., which stated that the high CRP along with increased ferritin level was associated with the severity of COVID-19 infection in addition of pre-existing comorbidities such as hypertension, cardiovascular disease, diabetes mellitus and kidney failure. The median CRP on the study was 136.0 mg/L while the median of the ferritin was 811 mcg/L.[8] Ferritin and CRP were acute phase proteins used as inflammation marker, and the increase of ferritin level correlated with severity degree of COVID-19 which was associated with cytokine storm and immune response.[10] Suzuki et al., showed that ferritin and CRP levels were

lower in the Omicron group than in the Delta group that correlated with the milder symptoms in Omicron phase.[17] Wang also found that ferritin and CRP levels had the highest value in the Delta group compared to B.1.338 group and Omicron group.[18]

This study result showed that the best cut-off value for ferritin level was 963.1 mcg/L which was considered very excellent for severe disease. This result was in accordance with study result by Gandini et al., who published ferritin cut-off value of 500 mcg/L for severe COVID-19 patients group.[11] Based on a study by Zhou et al*.,* the ferritin level in severe COVID-19 significantly increased on 4th day and reached its peak in 16th day.[10] Increased ferritin level was presumably associated with incidence of cytokine storm categorized in hyperferritinemia syndrome, and was associated with inflammation in COVID-19 infection; thus, ferritin might be utilized to predict the severity degree of the disease and the extent of cytokine storm.[19] Ferritin occurs as a cytosolic protein in most tissues, although a mitochondrial form also exists and nuclear localization has been proposed. Even though widely recognized as a representative of total body iron stores, its prognostic utility is linked with acute and chronic inflammatory processes and is nonspecifically raised in a variety of such disorders, including chronic kidney disease, rheumatoid arthritis, and autoimmune disorders, etc.[12]

Several studies have varied cut-off value for CRP level ranged from 1-10 mg/dL on severe COVID-19 group which was correlated with severity degree in the patients.[11,12,16,20] This study result showed that the optimum cut-off value for CRP was 7.65 mg/dL in order to predict severe degree of COVID-19 infection. C-reactive protein increased rapidly during acute inflammation within the first 608 hours and significantly peaked after 48 hours, declining afterwards as the inflammatory response resided.[3,6] Moreover, the timing of CRP increase should be taken into account since the time was shorter compared with ferritin and that there were other factors which affected CRP levels, including liver damage, history of administered treatments and timing of CRP level examination.[9]

Ferritin has sensitivity of 93.3% and specificity of 80.0%, thus, could be categorized as good validity, while CRP has sensitivity of 76.7% and specificity of 63.3%, thus, could be categorized as low validity. The limitation on this study was that on the moderate and severe cases, the comorbidities were not equally proportioned, which potentially may confound the study result.

In conclusion, validity of ferritin level was more superior than CRP and was presumably associated with incidence of cytokine storm. This study could be further advanced by accounting the proportion of comorbidities in moderate and severe COVID-19 groups.

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