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INDONESIAN JOURNAL OF ANESTHESIOLOGY AND REANIMATION
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Original Article

EFFECT OF SNAKEHEAD FISH AND SEA CUCUMBER EXTRACT ADMINISTRATION ON MAST CELL INFILTRATION, INTERLEUKIN-6 (IL-6), AND ALBUMIN LEVELS IN BURNS AND SURGICAL WOUNDS

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ABSTRACT

Introduction: Burn injury impairs almost every organ system, which causes significant morbidity and mortality. Meanwhile, the phases included in burn healing are inflammation, cell recruitment, matrix deposition, epithelialization, and tissue remodeling phase. Previous studies showed that snakehead fish and sea cucumber extract have these effects and are beneficial in burn and post-surgery wounds. **Objective:** This study aims to analyze the effect of snakehead fish and sea cucumber extract supplementation towards mast cell infiltration, IL-6, and albumin level in burn and post-surgery wounds. **Materials and Methods:** A double-blind randomized control trial was carried out at Dr. Moewardi Hospital Surakarta in November 2017 on 30 subjects, which were divided into 2 groups. Mast cell infiltration was observed on burn and post-surgery wounds colored with Toluidine Blue, while IL-6 and albumin were measured -blood, where both groups had comparable basic characteristics. **Results and Discussion:** There was a statistically insignificant (p=0.835) higher increase in albumin level in the treatment group, while an insignificant (p=0.056) greater decrease also occur in the IL-6 level. The decrease in cell mast infiltration after treatment was also higher and not statistically significant (p=0.526). Previous studies showed that amino acids from snakehead fish play an important role in wound healing. Meanwhile, high EPA content in sea cucumber is due to its ability as an Echinodermata to regenerate tissue. It was also discovered that the results available about sea cucumber and sea snake extract on wound healing are different based on the skin condition after the use of the extracts. **Conclusion:** Snakehead fish and sea cucumber extract supplementation can increase albumin level, decrease IL-6 level and mast cell infiltration in burn or post-surgery wounds.

Keywords: Albumin; Burn; IL-6; Mast Cell Infiltration; Snakehead Fish and Sea Cucumber Extract; Wound Incision

ABSTRAK

Pendahuluan: Luka bakar merupakan luka sangat traumatis karena melemahkan hampir setiap sistem organ sehingga menyebabkan morbiditas dan mortalitas yang signifikan. Terdapat beberapa fase dalam penyembuhan luka bakar, yaitu fase inflamasi, rekrutmen sel, deposisi matriks, epitelisasi dan remodelling jaringan. Ekstrak ikan gabus dan teripang dipikirkan dapat mencapai efek-efek tersebut sehingga menguntungkan bagi penyembuhan pasien luka bakar dan luka operasi. **Tujuan:** Peneliti menulis penelitian ini untuk menganalisis pengaruh pemberian ekstrak ikan gabus dan teripang terhadap infiltrasi sel mast, kadar IL-6, dan albumin darah pasien luka bakar atau luka pasca operasi. **Bahan dan Metode:** Penelitian dengan desain double blind randomized control trial dilakukan di RS Dr. Moewardi Surakarta pada 30 subjek, dimulai pada bulan November 2017. Subjek dibagi kedalam dua kelompok. Infiltrasi sel mast diamati pada kerokan luka bakar atau luka operasi yang diwarnai dengan Toluidine Blue, sedangkan kadar IL-6 dan albumin diukur dari darah pasien. Kedua kelompok memiliki karakteristik dasar yang homogen. **Hasil dan Pembahasan:** Terjadi peningkatan kadar albumin yang lebih tinggi pada kelompok perlakuan, namun tidak bermakna secara statistik (p=0,835). Selain itu, terjadi penurunan kadar IL-6 yang lebih besar pada kelompok perlakuan meskipun tidak bermakna secara statistik (p=0,056). Demikian juga penurunan infiltrasi sel mast sesudah perlakuan lebih tinggi pada kelompok perlakuan, namun tidak bermakna secara statistik (p=0,526). **Kesimpulan:** Pemberian ekstrak ikan gabus dan teripang meningkatkan kadar albumin dan menurunkan kadar IL-6 dan infiltrasi sel mast pada pasien luka bakar atau luka operasi.

Kata Kunci: Albumin; Luka Bakar; IL-6; Infiltrasi Sel Mast; Ekstrak Ikan Gabus dan Teripang; Luka Operasi

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INTRODUCTION

Wound healing is a complicated process, which consists of 3 phases, namely inflammation, proliferation, and maturation. The inflammation phase is preceded by hemostasis and inflammation that lasts for at least 7 days. Meanwhile, the proliferation phase is marked with epithelization, angiogenesis, granulation formation, and collagen deposition, which starts at least 3 days after injury and lasts for approximately 7 days. The maturation phase has transitional characteristics from granulation tissue into scar formation. This phase starts from the 7th day and may last for several weeks (1). During normal wound healing, the monocyte changes into macrophage after infiltration, while at the end of the inflammation phase, the inflammation signal subsides and finally stops. This is important because prolonged inflammation causes chronic wound healing. Therefore, reducing the production or release of NO, PGE_2, and other cytokines such as TNF-α, IL-1β, IL-6, and COX-2 is a good strategy to prevent prolonged inflammation (2). In the study by Zohdi RM et al, rats with burn injury were treated with sea cucumber-based hydrogel and showed significant wound healing. It had lower levels of IL-1α, IL-1β, and IL-6 compared to the control group. Meanwhile, lower pro-inflammatory cytokines make better wound healing (3). According to Ab Wahab SZ et al, wound healing in cesarean section patients treated with snakehead fish extract gave significant results. This was due to higher amino acids such as glycine and fatty acids such as arachidonic acid, which are involved in wound healing through collagen re-modeling and wound re-epithelialization mechanism (4).

Treatment using snakehead fish and sea cucumber extract in burn and post-surgery wounds is assumed to reduce the inflammation process, help in re-modeling and re-epithelialization, as well as quicken wound healing. In addition, they are also assumed to increase the albumin levels.

MATERIALS AND METHODS

This study was conducted from March to July 2018 in the Central Surgery Installation and inpatient care of Dr. Moewardi Hospital, Surakarta, after the ethics committee acceptance. It was a double-blind randomized controlled trial with 35 subjects, where 5 were dropped out (3 had nausea and vomiting, while the other 2 had deteriorating conditions). After randomization, a total of 15 subjects were treated with snakehead fish and sea cucumber extract, while the other 15 were treated with placebo. Inclusion criteria were 18-65 years old male or female subjects with burn injury or post-surgery wound, have received treatment in inpatient care, High Care Unit, or Intensive Care Unit, burned surface area of 10-50% or post-laparotomy wound, and consented to be the subjects of the study. Exclusion criteria were allergy to snakehead fish and sea cucumber extract, electrical burn injury, severe liver disease such as cirrhosis, and malignancy. Drop-out criteria were deteriorating condition and death.

RESULTS AND DISCUSSION

Based on Table 1, the characteristics of patients with burn injury and post laparotomy are insignificantly different, which showed that their characteristics are homogenous.

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Table 1. Characteristics of Study Subjects

Characteristics	Group		p-value
	K1	K2	
Sex[b]			0.269
Male	5(33.3%)	8(53.3%)	
Female	10 (66.7%)	7 (46.7%)	
Age[a]	44.13±11.50	41.47±13.79	0.57
Weight[a]	56.47±8.54	51.87±5.41	0.089
Height[a]	164.40±3.60	164.73±3.92	0.81
BMI[c]			0.282
Underweight	5 (33.3%)	7 (46.7%)	
Normal	8 (53.3%)	8 (53.3%)	
Overweight	2 (13.3%)	0 (0.0%)	

[a] independent sample T-test (unpaired, normal distribution)
[b] Chi-square test (unpaired, nominal data)
[c] Mann Whitney test (unpaired, ordinal data)

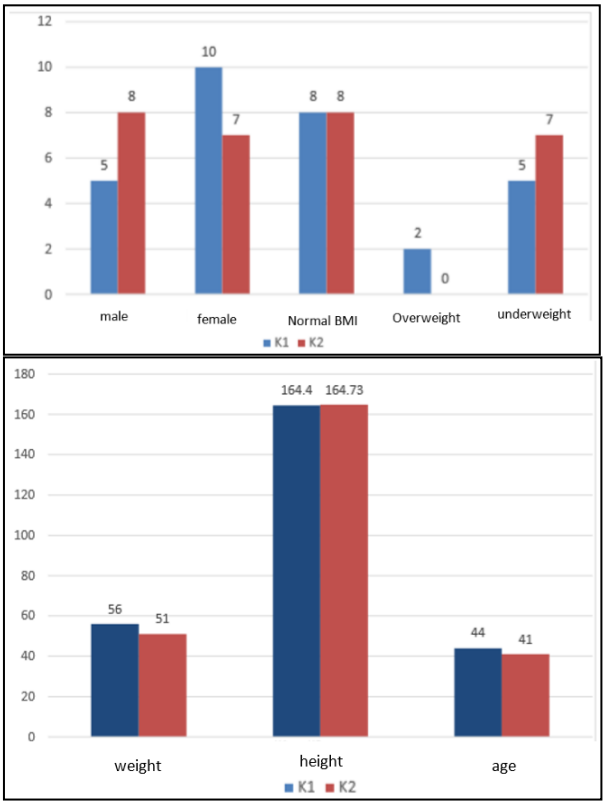

Figure 1. Characteristics of Study Subjects

From Table 2, the difference between albumin level before and after treatment (pre-test and post-test) are better than the control group with a p-value of 0.835 (p>0.05). Meanwhile, this value showed that the difference is not significant.

Table 2. The Difference on Albumin Level in Snakehead Fish and Sea Cucumber Extract Treatment Compared to Control Group

Group	Albumin			p-value
	Pre-test	Post-test	Δ	
Group 1	2.87±0.56	2.97±0.47	0.10±0.36	0.298[c]
Group 2	2.77±0.53	2.99±0.45	0.22±0.49	0.103[c]
p-value	0.618[a]	0.906[a]	0.835[b]	

[a] independent sample T-test (unpaired, normal distribution)
[b] Mann Whitney (unpaired, abnormal distribution)
[c] paired sample T-test (paired, normal distribution)

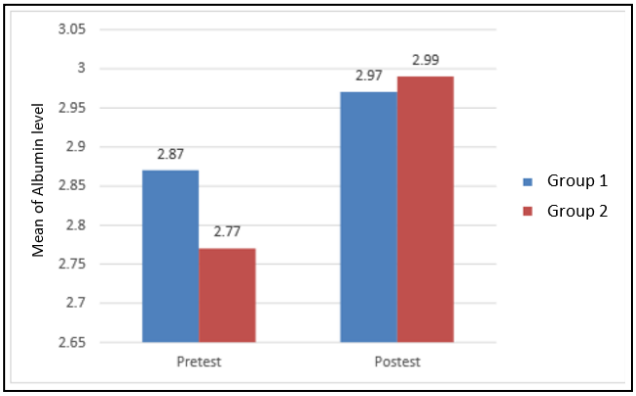

Figure 2. The Difference on Albumin Level in Snakehead Fish and Sea Cucumber Extract Treatment Compared to Control Group

Table 3. The Difference on IL-6 Level in Snakehead Fish and Sea Cucumber Extract Treatment Compared to Control Group

Group	IL-6			p-value
	Pre-test	Post-test	Δ	
Group 1	249.78 ±170.93	171.7 ±136.27	-78.09 ±160.08	0.027[d]
Group 2	400.24 ±163.35	204.59 ±148.65	-195.65 ±162.51	<0.001[c]
p-value	0.020[a]	0.443b	0.056[a]	

[a] Independent sample T-test (unpaired, normal distribution)
[b] Mann Whitney (unpaired, abnormal distribution)
[c] Paired sample T-test (paired, normal distribution)
[d] Wilcoxon test (paired, abnormal distribution)

From Table 3, the treatment group has a greater decrease of IL-6 level compared to the control group, however, it is statistically insignificant.

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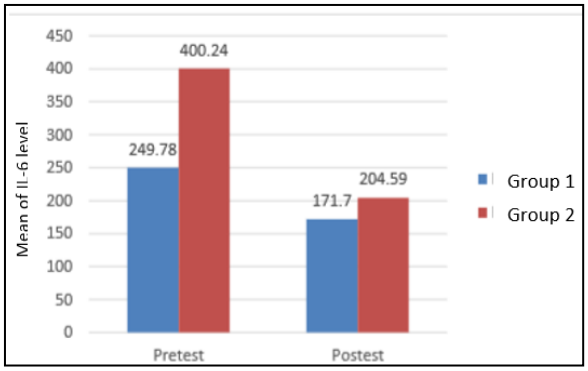

Figure 3. The Difference on IL-6 Level in Snakehead Fish and Sea Cucumber Extract Treatment Compared to Control Group

Based on Table 4, there was a statistically insignificant difference in the treatment group with a greater decrease of mast cell infiltration compared to the control group.

Table 4. The Difference on Mast Cell Infiltration in Snakehead Fish and Sea Cucumber Extract Treatment Compared to Control Group

Group	IL-6			p-value
	Pretest	Posttest	Δ	
Group 1	12.53±6.08	10.60 ±7.15	-1.93±10.19	0.474[d]
Group 2	16.80 ±8.79	12.40±7.03	-4.40 ±10.82	0.138[c]
p-value	0.133[a]	0.493b	0.526[a]	

[a] independent sample T-test (unpaired, normal distribution)
[b] paired sample T-test (paired, normal distribution)

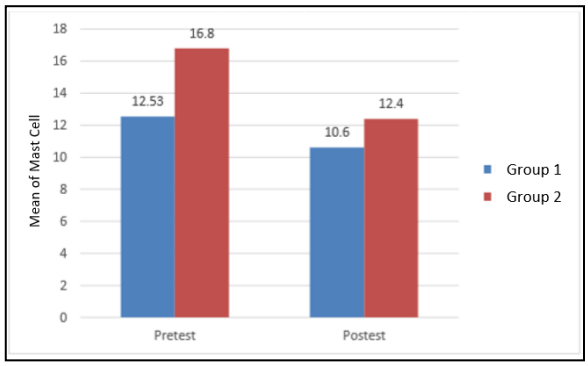

Figure 4. The Difference on Mast Cell Infiltration in Snakehead Fish and Sea Cucumber Extract Treatment Compared to Control Group

Previous studies showed that amino acids such as glycine, glutamine, and arginine from snakehead fish play important role in wound healing. Although the capsules of albumin from snakehead fish extract are effective in increasing albumin level and reducing pitting edema, they do not affect the length of stay in patients with severe preeclampsia who passed through cesarean section (5). This is different from sea cucumber (Stichopus chloronatus), which contained fatty acids such as arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) that are potentially used in tissue repair and wound healing. Similarly, high EPA content in sea cucumber is based on its ability as an Echinodermata to regenerate tissue. Most of its wall protein, approximately 70% consists of collagen, which is an important component for connecting tissue (6).

The study by Siti Zubaidah Ab Wahab et al. on the treatment of post-Caesarian section patients using Channa striatus extract compared to placebo gave an insignificant ($p< 0.511$) result after 3 days and also ($p< 0.538$) after 6 weeks post-surgery (4). These were different from the results of Zohdi RM et al., where rats with burn injury were treated with topical sea cucumber hydrogel, and their levels of pro-inflammatory cytokine (IL-1α, IL-1β, and IL-6) were reduced significantly on the 7th day (3). Yamanaka H et al. also examined the effect of Collagen Peptide (nutritional drink with 10 g of collagen) treatment on pressure ulcer healing compared to the control group. The results were significant in wound evaluation such as depth, granulation, exudate, size, inflammation/ infection, necrotic tissue, albumin level, pre-albumin, and other parameters in the treatment group compared to the control after 4 weeks. Meanwhile, a recommended guideline published by the Japanese Society of Pressure Ulcer on the prevention and management of ulcer pressure with collagen peptide for supplemental nutrition is currently at level C1 due to limited data (7).

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The study by Proksch E et al. on skin elasticity after oral collagen supplementation for 4 weeks compared to the control group showed that patients with 2.5 g and 5 g of collagen supplementation had better skin elasticity (7). Koyama Y also published a few clinical studies on the effect of supplemental collagen peptide (CP) in Japanese. Based on the results of the double-blind controlled trial using a placebo, it was discovered that daily consumption of 5 g CP increased the elasticity of face skin and reduced ultraviolet-induced skin erythema. There was also an increase in T cell-related immunity in Japanese with chronic fatigue after 10 g of CP daily for 8 weeks (8).

CONCLUSION

Patients treated with snakehead fish and sea cucumber extracts had a greater increase in albumin level and a higher decrease in IL-6 level as well as mast cell infiltration compared to the control group. However, the results were statistically insignificant due to the short duration of treatment. In other similar studies about collagen's effect on wound healing, these extracts need to be administered for 4 weeks.

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Original Article

ACUTE KIDNEY INJURY FOLLOWING CORONARY ARTERY BYPASS GRAFTING WITH CARDIOPULMONARY BYPASS AT DR. SOETOMO GENERAL ACADEMIC HOSPITAL SURABAYA: A PRELIMINARY STUDY

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ABSTRACT

Introduction: Acute Kidney Injury (AKI) is a significant cause of morbidity and mortality following common cardiac surgery. The most common cardiac surgery performed at Dr Soetomo General Academic Hospital Surabaya is coronary artery bypass grafting (CABG). Along with the increasing number of these procedures performed on subjects, Cardiopulmonary Bypass (CPB) has also grown in popularity, which is frequently associated with postoperative AKI. **Objective:** To investigate the incidence of postoperative AKI in subjects who had undergone a CABG procedure using the CPB technique. **Materials and Methods:** A retrospective study was conducted at Dr. Soetomo General Academic Hospital in Surabaya. All subjects who had CABG with CPB in 2019 were included in the study. The incidence of AKI was determined by comparing the creatinine serum level before and after surgery on days 0, 1, 2, 3, and >3 according to the AKIN criteria. **Results and Discussion:** The 68 subjects who underwent the CABG with CPB procedure were made up of 53 males (77.9%) and 15 females (22.1%). The average age of the subjects was 58.209.07. This study included 63 subjects (five subjects could not be evaluated due to incomplete data), and AKI was diagnosed in 44 of them using the AKIN criteria (69.8%). Postoperative AKI was reported in 14 subjects (22.2%) on day 0, 18 subjects (28.6%) on day 1 post-operation, and the same number of 6 subjects (9.5%) on day 2 and day 3 post-operation. None of them had AKI after the third post-operative day. **Conclusion:** More than 50 % of cases of post-CABG Acute Kidney Injury (AKI) occur at Dr. Soetomo General Academic Hospital, with the majority occurring on the first day after surgery.

Keywords: Acute Kidney Injury; CABG; Cardiovascular Disease; CPB; Postoperative Cardiac Surgery

ABSTRAK

Pendahuluan: Seiring dengan peningkatan *Coronary Artery Bypass Grafting* (CABG), teknik *Cardiopulmonary Bypass* (CPB) juga lebih sering digunakan. Tindakan ini adalah operasi jantung yang paling umum dilakukan di RSUD Akademik Dr. Soetomo Surabaya. Hal ini sering menyebabkan *Acute Kidney Injury* (AKI) pascaoperasi. Beberapa kondisi terkait dengan kejadian AKI pasca CPB. **Tujuan:** Untuk mengetahui kejadian AKI pascaoperasi pada pasien yang telah dilakukan CABG dengan teknik CPB. **Bahan dan Metode:** Penelitian ini merupakan penelitian deskriptif retrospektif di RSUD Dr. Soetomo Surabaya. Semua pasien yang menjalani CABG dengan CPB pada tahun 2019 diteliti. Kejadian AKI dievaluasi dengan membandingkan kadar kreatinin serum sebelum dan sesudah operasi pada hari ke 0, 1, 2, 3, >3 menggunakan kriteria AKIN. **Hasil dan Pembahasan:**Ada 68 pasien yang menjalani teknik CPB, 53 pasien (77,9%) berjenis kelamin laki-laki dan 15 pasien (22,1%) berjenis kelamin perempuan. Usia rata-rata pasien adalah 58,20 ± 9,07. Diantaranya, 44 pasien (69,8%) dari 63 memenuhi kriteria AKI berdasarkan kriteria AKIN. Lima pasien tidak dapat dievaluasi karena data yang tidak lengkap. Empat belas pasien (22,2%) mengalami AKI pascaoperasi pada hari ke 0, 18 (28,6%) pada hari 1 pascaoperasi, dan 6 pasien (9,5%) didiagnosis AKI pada hari ke 2 dan ke 3 pascaoperasi. **Kesimpulan:** Angka kejadian AKI pasca CABG dengan CPB di RSUD Dr. Soetomo lebih dari separuh dari total kasus yang dikerjakan, dan sebagian besar terjadi pada hari pertama pascaoperasi.

Kata kunci: *Acute Kidney Injury*; CABG, Penyakit Kardiovaskular; CPB; Pascaoperasi Bedah Jantung

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INTRODUCTION

Coronary Artery Bypass Grafting (CABG) is a procedure that replaces an occluded coronary artery with arteries or veins from other parts of the patient's body in order to restore normal blood flow (1). This is the most common type of thoracic and cardiovascular surgery in the world (2). There was no national data on the epidemiology of the procedure in Indonesia. The total number of CABG procedures performed in Dr. Soetomo General Academic Hospital Surabaya in 2018 and 2019 is 82 and 68, respectively.

Cardiopulmonary bypass (CPB) is a surgical technique in which a machine temporarily replaces the heart and lung function, maintaining blood circulation and oxygen levels; thus, heart surgery can be performed (3). This technique may contribute to the occurrence of AKI due to the systemic inflammatory response, disruptions in regional blood flow, renal vasomotor tonus, and microemboli formation (3). AKI can be caused by kidney diseases (such as acute interstitial nephritis, acute glomerulosclerosis, and vasculitis kidney disease) as well as abnormalities outside the kidney (such as prerenal azotemia and postrenal obstructive nephropathy). AKI can also be caused by acute lung failure or an acute coronary syndrome. All of these conditions may contribute to direct kidney injury, which can lead to kidney failure (1).

To characterize and analyze AKI, the majority of the studies employed the Acute Kidney Injury Network (AKIN) standards. These measurements are based on serum creatine levels or an adjustment of serum creatinine (expanded by roughly 1.5 times the benchmark) and pee yield (0.5 ml/kg/h for approximately 6 hours). The limitation of these standards is their use without revision for serum creatinine changes inferable from liquid equilibrium during a liquid revival at CPB technique, which leads to underdiagnosis of AKI (4). The advantage of using these criteria is that AKI is calculated without the need for urine output, and AKIN only encompasses three days of hospitalization.

Table 1. AKI criteria based on AKIN (2).

AKI degree	Urine production	AKIN
1	<0.5 mL/kg/hours in 6-12 hours	Creatinine serum 1.5-2x baseline level or an increase ≥0.3 mg/dL for 48 hours
2	<0.5 mL/kg/hours in >12 hours	Creatinine serum >2-3x baseline level
3	<0.3 mL/kg/hours in >24 hours or anuria for >12 hours	Creatinine serum >3.0x baseline level or an increase >4.0 or RRT

Silva et al. conducted a forthcoming accomplice investigation on adult subjects who underwent CABG. When serum creatinine fixation and pee yield were both used, AKI occurred in 83.3 % of the 198 subjects. By AKIN using serum creatinine concentration alone, the frequency of AKI was 27.3 %. The use of pee yield to analyze AKI from AKIN measures was significant (3). According to other studies, the incidence rate of AKI after heart surgery was 49 % (81.63 % class I AKIN) on day 2 post-surgery based on

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AKIN criteria (2). According to Amini et al., 15.8% of subjects developed AKI (275 out of 1737 subjects). Subjects with AKI had a longer ventilation time, ICU stay, and medical clinic stay (P 0.001). Death rates in subjects with and without AKI were 28 (10.2%) and 22 (1.5%), respectively (P 0.001) (4).

CPB with >70 minutes and cross-clamp time >60 minutes increase the risk of AKI after heart surgery by OR of 4.76 and 2.84, respectively (p0<05) (5). On day 60, the mortality rate after severe AKI with the need for renal transplantation was 52.6 %, and on day 90, it was 44.7 %. Another findings revealed that the mortality rate on day 30 in AKI patients who required renal transplantation after heart surgery was 58.6 % (6). CABG was performed on approximately 22-57 % of all hospitalized subjects suffering from AKI (7).

The following conditions were associated with an increased risk of post-CPB AKI: 1) Old age and female sex; 2) pre-operative heart disease; 3) emergency surgery; 4) peripheral arterial disease; 5) repeated intervention; 6) insulin-dependent diabetes; 7) intraoperative aprotinin use; 8) chronic obstructive pulmonary disease (COPD); and 9) pre-operative renal disfunction (6,8,9).

Cho et al. revealed that 23.9 % of subjects had AKI despite having a normal preoperative renal capacity. Indeed, even with early recovery of renal capacity within 3 days, AKI increased the risk of Acute Kidney Disease (AKD) (OR 3.21, 95 % CI 1.98–5.20, P0.001) and Chronic Kidney Disease (CKD) (OR 2.86, 95 % CI 1.68–4.86, P0.001), while persistent AKI increased the risk of AKD (OR 12.07, 95 % CI 5.56–26.21, P0.001) and CKD (OR 10.54, 95 A multivariable analysis identified CPB is needed as a preventive approach to reduce the number of the incidence of AKI. 3-month postoperative cardiovascular breakdown and high right ventricular systolic pressing factor as free risk factors for CKD (10). Preoperative renal function is a risk factor for postoperative AKI. Preoperative kidney work has an impact on outcomes because impaired renal capacity prior to a medical procedure leads to more regrettable consequences such as a longer length of hospitalization and a higher mortality rate (11).

From 2000 to 2010, the number of mortalities caused by cardiovascular methods increased by 28%. Up to half of the subjects who underwent heart medical procedures with CPB are predisposed to severe kidney injury. Cardiac Surgery-Associated Acute Kidney Injury (CSA-AKI) patients who require Renal Replacement Therapy (RRT) have a death rate of up to 60%. The frequency is increasing in conjunction with the heinous death rate. This increased the length of medical clinic stay as well as other long-term outcomes such as persistent kidney disease, death rate, and emergency clinic costs. As a result, it is critical for an early conclusion to direct procedures to protect renal capacity (12).

The CPB technique has become more popular as the number of CABG procedures performed in subjects has increased. The number of CABG surgeries in Indonesia is expected to rise in the coming years due to improvements in hospital facilities and an increase in the number of cardiothoracic surgeons. Dr. Soetomo General Academic Hospital Surabaya has performed heart surgeries since 1960, and the number of procedures has continued to rise to the present day (13). Therefore, identification of risk factors causing AKI following

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This study was aimed to investigate the incidence of postoperative AKI in subjects who underwent CABG with CPB.

MATERIALS AND METHODS

This was a retrospective descriptive study performed at Dr. Soetomo General Academic Hospital Surabaya. The study included all subjects who had a CABG with CPB technique performed during surgery at Dr. Soetomo General Academic Hospital Surabaya in 2019. All subjects who had CABG with CPB technique at Dr. Soetomo General Academic Hospital Surabaya met the inclusion criteria. All data, such as CPB duration and creatinine level before and after surgery, were obtained from a medical record. Subjects with incomplete data in their medical records were excluded. The incidence of AKI was assessed using the AKIN criteria. The Research Ethics Committee of Airlangga University's Faculty of Medicine approved this preliminary study. Each patient's personal information was kept private and was only used for research purposes.

The incidence of AKI was determined by comparing creatinine serum levels before and after surgery on days 0, 1, 2, 3, and >3, according to AKIN criteria. Meanwhile, the Cockcroft-Gault formula was used to calculate eGFR (14).

$$CrCl\left(\frac{mL}{minute}\right) = \frac{(140 - age)x\ \text{body weight (kg)}}{Creatinine\ serum\ \left(\frac{mg}{dl}\right) x\ 72}\ (x0.85\ in\ female)$$

Tables were used to display the univariate data. The numeric data was shown in minimum and maximum values and mean ± deviation standard. The categorical data were presented in the form of a frequency and percentage (%).

RESULTS AND DISCUSSION

At Dr. Soetomo General Academic Hospital Surabaya, 68 patients underwent CPB surgery. Males made up 77.9% of the 53 subjects, while females made up 15%. (22.1 percent). The diagnosis of subjects who underwent CPB surgery varied, but the majority were diagnosed with CAD-TVD (45 subjects: 66.2 %) (Figure 1). According to the patient distribution, the mean age was 58.2 ±9.07, with the youngest being 30 years old and the oldest being 83 years old. The shortest CPB session lasted 61 minutes, while the longest lasted 243 minutes. Preoperative creatinine serum levels ranged between 0.6 and 2.4747. The postoperative creatinine serum level was 0.59 at the lowest and 6.0 at the highest (Table 2).

According to the findings of this study, the shortest CPB duration among 65 subjects was 61 minutes, while the longest was 243 minutes. The average duration was 123.98±38.16. According to the data, the average duration of CPB was 123 minutes, increasing the risk of postoperative AKI. The duration of CPB was one of the risk factors for postoperative AKI. A CPB duration of more than 8 hours increases the risk of AKI by fourfold (8,15). A longer time in CPB may result in hemostatic disorders, increasing transfusions and limiting oxygen transport, which will stimulate inflammation mediators, causing kidney disruption (16,17). Several studies found that a prolonged cumulative CPB period (>180 minutes) was associated with a higher mortality rate, postoperative complications, intensive care unit length of stay, and length of mechanical ventilation. As a result, the recommended CPB/grafting time and cumulative CPB time should be less than 56 minutes and 180 minutes, respectively, to avoid the aforementioned side effects (18).

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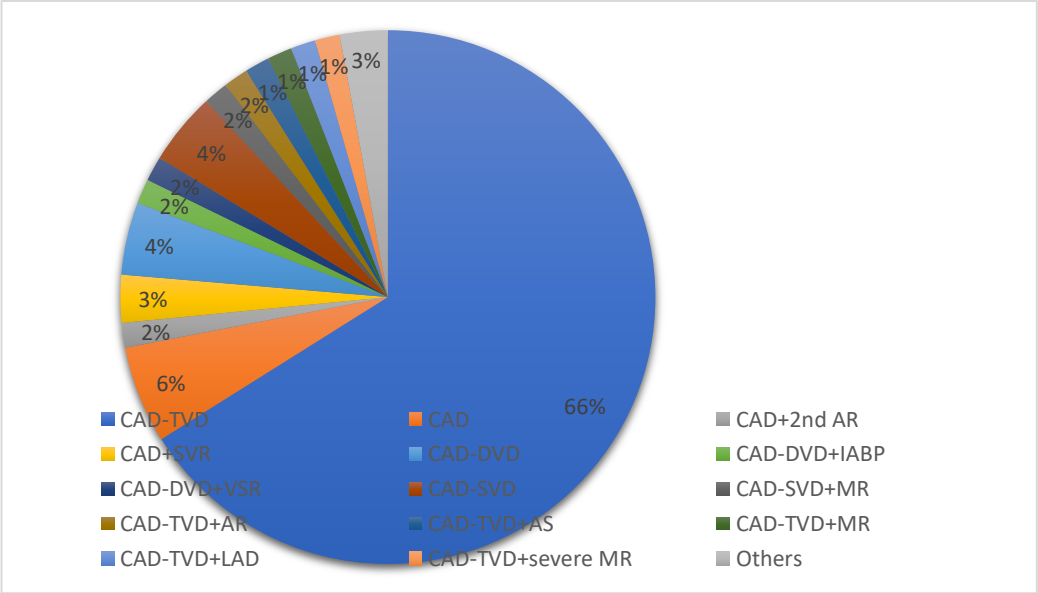

Figure 1. Frequency of surgery with CPB technique based on the diagnosis

Five of the 68 subjects who met the inclusion criteria had incomplete data, so they were unable to be evaluated for this study. AKI was diagnosed in 38 of the 63 subjects studied (60.3 %) based on AKIN criteria, which is more than the number of subjects who were not diagnosed with AKI (19 subjects, 39.7%). The incidence of AKI after heart surgery was assessed on postoperative days 0, 1, 2, and 3. Out of 44 subjects with AKI, 14 (22.2%) were diagnosed on postoperative day 0, 18 (28.6%) on postoperative day 1, 6 (9.5%) on postoperative day 2, 6 (9.5%) on postoperative day 3, and none were diagnosed after postoperative day 3 (Table 3).

Acute kidney injury (AKI) is characterized by a rapid decrease in kidney function over a period of hours to days. AKI was identified by an increase in creatinine serum and blood urea nitrogen (BUN) levels, as well as a decrease in urine production (19). AKI was classified using an increase in creatinine serum and urine production based on AKIN criteria (14). The mechanism of AKI development in CPB was connected to a decrease in renal perfusion (low flow hypoperfusion, low pressure no pulsatile perfusion) caused by vasoconstriction. The vasoconstriction was caused by the activation of free radicals, complement, inflammation mediators, decreased cardiac output (hypotension), and RAAS (2).

Hemodilution and hypothermia resulted in low pressure and no pulsatile perfusion. The inflammatory response can keep afferent arteriole constriction going. Long-term hypotension can lead to renal compensation exhaustion, filtration reserve exhaustion, and endogenous and/or exogenous vasopressors increasing afferent arteriole resistance, resulting in decreased GFR. Oliguria may occur at this stage of prerenal azotemia; however, tubular function may still be intact. A longer ischemic period will result in tubular structure injury and cell disruption, preventing tubular with back leak into circulation. The phenomenon of oxidative injury and inflammation causes further hypoperfusion and damage in tubular cells (20).

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Table 2. Description of the characteristic of the patient and the risk factors

Variable	N	Minimum	Maximum	Mean±SD
Age	55	30	83	58.20±9.07
Bodyweight	63	39	90	66.48±11.85
Body height	63	143	176	161.86±6.32
CPB duration	65	61	243	123.98±38.16
Creatinine serum				
Preoperative	60	0.60	2.47	1.21±0.38
Postoperative D0	58	0.59	2.87	1.30±0.46
Postoperative D1	30	0.75	4.94	2.05±0.91
Postoperative D2	24	0.85	5.95	2.27±1.21
Postoperative D3	23	1	5	2.71±1.24
Postoperative D>3	21	1	6	2.33±1.39
eGFR				
Preoperative	55	20	201	73.58±32.09
Postoperative D0	53	15	252	70.15±38.41
Postoperative D1	29	7	94	47.86±21.27
Postoperative D2	23	6	149	44.91±30.28
Postoperative D3	21	9	61	35.76±13.82
Postoperative D>3	19	11	153	46.00±35.17

Notes:
D0: early postoperative
D1: postoperative day 1
D2: postoperative day 2
D3: postoperative day 3
D>3: postoperative after day 3
CPB: Cardiopulmonary Bypass

In this study, eGFR was found to decrease from post-surgery until the third day of surgery, after which it began to rise (Preop 73.58±32.09, 70.15±38.41, 47.86±21.27, 44.91±30.28, 35.76±13.82, 46.0±035.17). The Cockcroft-Gault formula was used to calculate the estimated glomerular filtrtration rate (eGFR). This formula used body weight to calculate creatinine clearance in mL/minute (21). Alteration in eGFR is connected to creatinine clearance from collected urine after 24 hours and Gentamycin clearance (22,23). A multicenter prospective study found that the Cockcroft-Gault formula could be used to predict the prognosis of a cardiovascular event, specifically mortality and bleeding (24). Nevertheless, in a diabetic patient, GFR calculated using the Cockcroft-Gault formula was overestimated (25).

Table 3. Description of the incidence of AKI

Variable	n (%)
Total AKI diagnosis (n = 63)	
AKI	44 (69.8)
No AKI	19 (30.2)
Postoperative AKI (n = 44)	
AKI D0	14 (22.2)
AKI D1	18 (28.6)
AKI D2	6 (9.5)
AKI D3	6 (9.5)
AKI D>3	0 (0)

Notes:
AKI: acute kidney injury (An increase of creatinine serum ≥0.3 or > 1.5 times baseline value / preoperative)
D0: early postoperative
D1: postoperative day 1
D2: postoperative day 2
D3: postoperative day 3
D>3: postoperative after day 3

Glomerular filtration rate (GFR) was an important factor in determining AKI incidence in post-cardiac surgery subjects. Preoperative eGFR is a risk factor for postoperative AKI, and subjects with a preoperative eGFR of 70 mL/min/1.73m^2 have a higher incidence of AKI (26). Meta-analysis study on eGFR value before CPB operation showed a correlation between low eGFR value with AKI where preoperative GFR of <30 mL/min/1.73m^2 was a risk factor of postoperative AKI and increases the risk of AKI for more than 4,000 times (8,15,26,27).

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This study has limitations, such as other risk factors for AKI after 48 hours that were not investigated; thus, we cannot conclude the etiology of AKI caused by perioperative-CABG on ICU subjects with elevated creatinine serum on postoperative day 3.

CONCLUSION

The majority of AKI situations were encountered on the first postoperative day. After postoperative day 3, there was no evidence of AKI. More studies with more complete parameters (creatinine serum and urine production) or using biomarkers for kidney injury, as well as analysis of other factors causing AKI and patient outcomes, are required so that we can gain a better understanding of AKI after CABG.

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Original Article

EUROSCORE II AS PREDICTOR OF MORTALITY AND MORBIDITY IN POST-CABG PATIENT IN DR. SOETOMO GENERAL ACADEMIC HOSPITAL

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ABSTRACT

Introduction: European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a scoring system to predict mortality risk after cardiac surgery. EuroSCORE II was introduced to replace and show superiority over EuroSCORE I which tends to overestimate the risk of heart surgery procedures and have a low discrimination ability. Meanwhile, this is the first study to analyze EuroSCORE II as a predictor of mortality and morbidity in Indonesians. **Objective:** This study aims to analyze EuroSCORE II as a predictor of mortality and morbidity in Indonesians. **Materials and Methods:** This is a retrospective study using medical records of CABG patients in Dr. Soetomo General Academic Hospital from January 2016 to December 2017. **Results and Discussion:** Out of 39 Patients who have performed CABG surgery, most were male (89.7%) with the highest age range of 46-65 years (59%). Deceased patients had an average EuroSCORE II of 22.36% and SD±26.97%7%, while 27 patients who survived had an average EuroSCORE II of 6.78% and SD±6.4%. Based on morbidity assessment, EuroSCORE II only accurately predicted the risk of kidney failure and did not properly assess the length of inotropic use, vasopressors, hospitalization time, the risk of arrhythmias, low cardiac output syndrome, Durante-operative bleeding, and the need for blood transfusion. These inaccuracies occurred because the samples that were included varied based on their standard deviation and pattern-less graph. **Conclusion:** EuroSCORE II is inadequate to predict morbidity and mortality in postoperative patients, therefore, it is considered less effective.

Keywords: Coronary Heart Disease; CABG; EuroSCORE II; Mortality; Morbidity

ABSTRAK

Pendahuluan: European System for Cardiac Operative Risk Evaluation (EuroSCORE) adalah sistem penilaian untuk memprediksi risiko kematian setelah operasi jantung. EuroSCORE II diperkenalkan untuk menggantikan dan menunjukkan keunggulan daripada EuroSCORE I. Perubahan ini karena EuroSCORE awal cenderung melebih-lebihkan risiko prosedur operasi jantung dan memiliki kemampuan diskriminasi yang rendah. Ini adalah studi pertama yang menilai EuroSCORE II sebagai prediktor mortalitas dan morbiditas pada populasi Indonesia. **Tujuan:** untuk menilai EuroSCORE II sebagai prediktor mortalitas dan morbiditas pada populasi Indonesia. **Metode dan Bahan:** studi retrospektif yang menggunakan rekam medis pasien CABG di Rumah Sakit Umum Dr. Soetomo selama Januari 2016 hingga Desember 2017. **Hasil dan Diskusi:** Dari 39 Pasien yang melakukan operasi CABG didominasi oleh pria (89,7%), untuk yang tertinggi rentang usia 46-65 tahun (59%), pasien meninggal memiliki rata-rata EuroSCORE II 22,36% dan standar deviasi ± 26,97%, 27 pasien hidup dengan rata-rata EuroSCORE II 6,78% dan standar deviasi ± 6, 4%. dalam menilai morbiditas, EuroSCORE II hanya tepat dalam meramalkan risiko gagal ginjal. Sementara EuroSCORE II tidak dapat digunakan dengan lama penggunaan inotropik, vasopresor, dan lama pasien di rumah sakit, risiko aritmia, sindrom cardiac output rendah, perdarahan selama operasi, dan kebutuhan transfusi darah. Hal ini dapat saja terjadi karena pada sampel ini memiliki variasi yang lebar dilihat dilihat dari standar deviasinya dan masing-masing

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grafik yang tidak berpola. **Kesimpulan:** Euroscore II tidak adekuat dalam memprediksi morbiditas dan mortalitas, oleh karena itu kurang efektif.

Kata kunci: Penyakit Jantung Koroner; CABG; EuroSCORE II; Mortalitas; Morbiditas

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INTRODUCTION

Coronary Heart Disease (CHD) is among the leading causes of mortality and morbidity globally, including Europe. The common approach to coronary revascularization for patients with blood vessels is Coronary Artery Bypass Graft (CABG) surgery due to its symptomatic and prognostic benefits (1). It has been shown that preoperative risk scores are important tools for risk assessment, cost-benefit analysis, and therapeutic trend study. Meanwhile, various scoring systems were also developed to predict mortality after adult cardiac surgery (2).

Since 1999, European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used worldwide as an assessment for mortality prediction. In 2011, EuroSCORE II was introduced due to the inadequate ability for discrimination of the previous assessment and its overestimation of cardiac surgery risk (3).

From September to November 1995 in 8 European countries, EuroSCORE was shown to affect mortality in 19,030 patients in 128 surgical centers (4). Meanwhile, between December 2011 and October 2012 in India, EuroSCORE II had a satisfying calibration power with good model compatibility in 537 patients who passed through cardiac surgery, including 498 patients eligible for EuroSCORE II calculations (5). In Pakistan, it is fairly good as a predictor of immediate postoperative mortality in low and medium-risk groups after cardiac surgery (6).

EuroSCORE II has not been used to assess mortality risk in Indonesia. Therefore, this study aims to assess EuroSCORE II as a predictor of mortality and morbidity in post-CABG patients and determine whether it can be used for the Indonesian population.

MATERIALS AND METHODS

This is a retrospective study analyzing EuroSCORE II as a predictor of mortality and morbidity in Indonesians. A total of 39 post-CABG patients in Dr. Soetomo General Academic Hospital, Surabaya, from January 2016 to December 2017 were included. The data such as age, sex, and EuroSCORE II were retrieved from medical records. Meanwhile, EuroSCORE II is composed of 3 major components, namely patients, cardiac, and operation-related factors.

Morbidity includes inotropic-vasopressor usage, length of stay, blood transfusion, arrhythmia risks, renal failure, low cardiac output syndrome, and Durante-operative bleeding. This study recorded demographic and clinical data, as well as the information needed to calculate the predicted risk of surgery using the additive European System for Cardiac Operative Risk Evaluation (7). Moreover, incomplete medical records are excluded.

RESULTS AND DISCUSSION

In this study, the demographic data were taken in form of gender and age. Based on the demographic characteristics of CABG patients in Dr. Soetomo General Academic Hospital as shown in Table 1, 89.7% of the 39 patients were male, while 10.3% were female.

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Furthermore, the highest age group was 46-65 years, which is 59% out of all age ranges.

Table 1. Demographic Characteristics of CABG Patients

Variable	Total (n=39)	Percentage (100%)
Gender		
Male	35	89.7%
Female	4	10.3%
Age		
26-45 years	5	12.8%
46-65 years	23	59%
>65 years	11	28.2%

The prevalence of CHD patients is higher in men than women for all age groups (8). From 2016 to 2017, most CHD patients were men (89.7%). In Iran, between 2017 and 2015, sex distribution from a total of 1,010 patients was 67.6% male and 32.4% female (9) (10).

Meanwhile, CHD is more prevalent in the age group of ≥ 40 years (10,11). The risk of CHD increases in males, the older age (age >40 years in men and >45 years in women), family history of CHD, smoking, hypertension (high blood pressure), diabetes, obesity, and low physical activity (12).

The 10% score of EuroSCORE II is the best cutoff in predicting postoperative mortality (10%, 15 from 920 patients, 1.6% compared to 10%, 23 from 107 patients, 21.5%, p<0,0001). This cutoff value has a sensitivity of 91.5%, specificity of 60.5%, a negative predictive value of 98.4%, and an accuracy of 90.3% (13). However, it was not effective enough in predicting patient mortality after CABG surgery. This is because, in this study, there were 9 patients with EuroSCORE II above 10%, while only one patient experienced postoperative mortality. Moreover, there was one patient with EuroSCORE II below 10% that did not survive due to cardiogenic shock and also all deceased patients were female. Barili et al reported that mortality incidence was significantly higher in women which were 17.3% compared to 9.8% in men, with a p <0.008. Based on standard deviation, both deceased and living patients had a fairly wide sample variation based on standard deviation, therefore, EuroSCORE II is not always appropriate in assessing mortality risk (14).

Table 2 shows that the mean EuroSCORE II for deceased patients was 22.36% with a standard deviation of ± 26.97% while living patients were 6.78% with a standard deviation of ± 6.4%. Although deceased patients had higher EuroSCORE II than the living, one died from cardiogenic shock with a low EuroSCORE II value of 3.29%.

Table 2. EuroSCORE II in assessing mortality risk in CABG postoperative patients

Mortality	Total (n=39)	EuroSCORE II Mean ± SD
Yes	2	22.36% ± 26.97%
No	37	6.78% ± 6.4%

Figure 1 shows a non-patterned graph of EuroSCORE II for the inotropic duration in each CABG postoperative patient. This is because patients with a lower EuroSCORE II of 17.17% had an inotropic duration of 28 days. Meanwhile, patients with a higher value of 41.43% did not use inotropic compared to patients with a lower EuroSCORE II.

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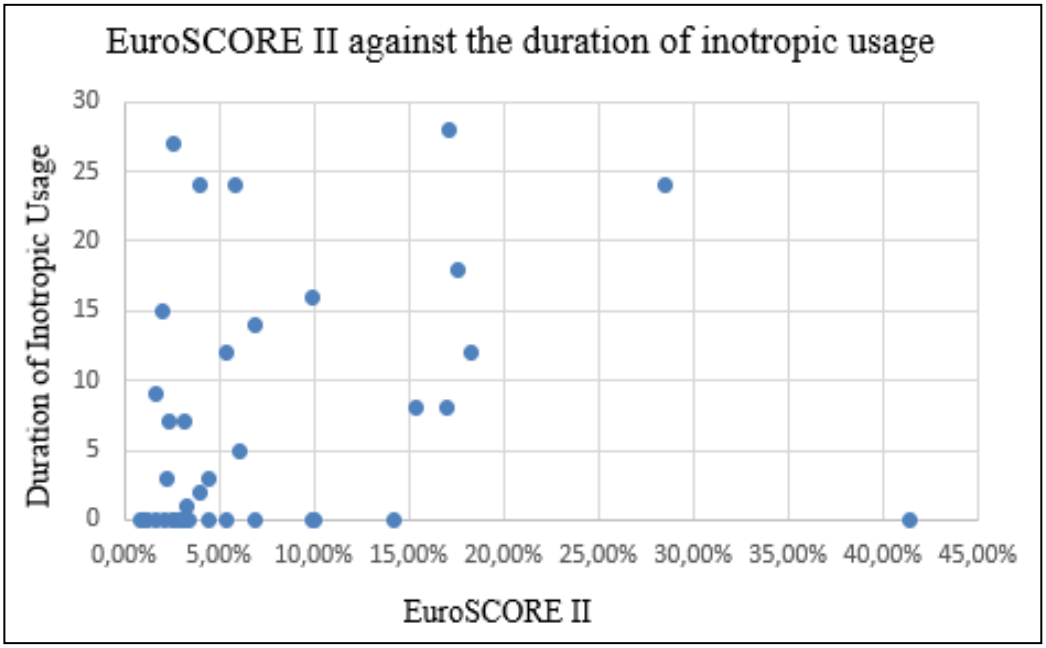

Figure 1. EuroSCORE II Against Inotropic Duration

Figure 2 shows a non-patterned graph of EuroSCORE II for the vasopressor duration in each CABG postoperative patient. This is because patients with a lower EuroSCORE II of 5.82% had a vasopressors duration for 36 days, while those with a higher value of 41.43% had a duration of 7 day.

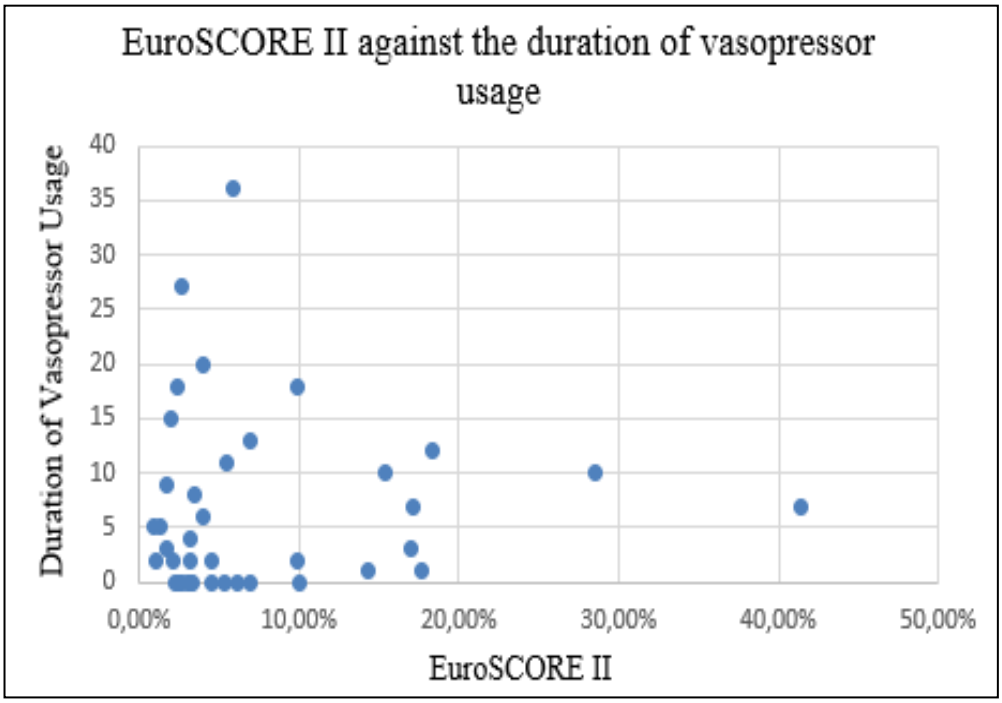

Figure 2. EuroSCORE II Against Vasopressors Duration

A previous study showed that EuroSCORE II is better at predicting inotropic duration (15). Biancari et al stated that EuroSCORE II with a score of 10% or greater

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is a strong predictor of prolonged inotropic use with a value of 67.3% compared to 25.0%, p<0.0001 (13). However, both Figures 1 and 2 show a pattern-less graph between EuroSCORE II and the duration of inotropic and vasopressors use. This is because patients with low EuroSCORE II as shown in the graphs did not always have a short duration of inotropic and vasopressor use. However, some had a long duration of use that exceed patients with higher EuroSCORE II.

Figure 3 shows a non-patterned graph of EuroSCORE II for the length of stay in hospital in each CABG postoperative patient. Based on the graph, patients with a low EuroSCORE II of 2.64% pass through 43 days of hospitalization, while those with a higher value of 41.43% had less length of stay, which was 31 days.

A pattern-less graph is also shown between EuroSCORE II and the length of hospitalization, which indicated that EuroSCORE II has low discriminatory power in predicting the length of hospitalization. In Iran, EuroSCORE II can not be used as the only assessment for risk estimation in CABG postoperative patients due to discriminatory power in predicting early morbidity, length of stay in the hospital, and ICU (16).

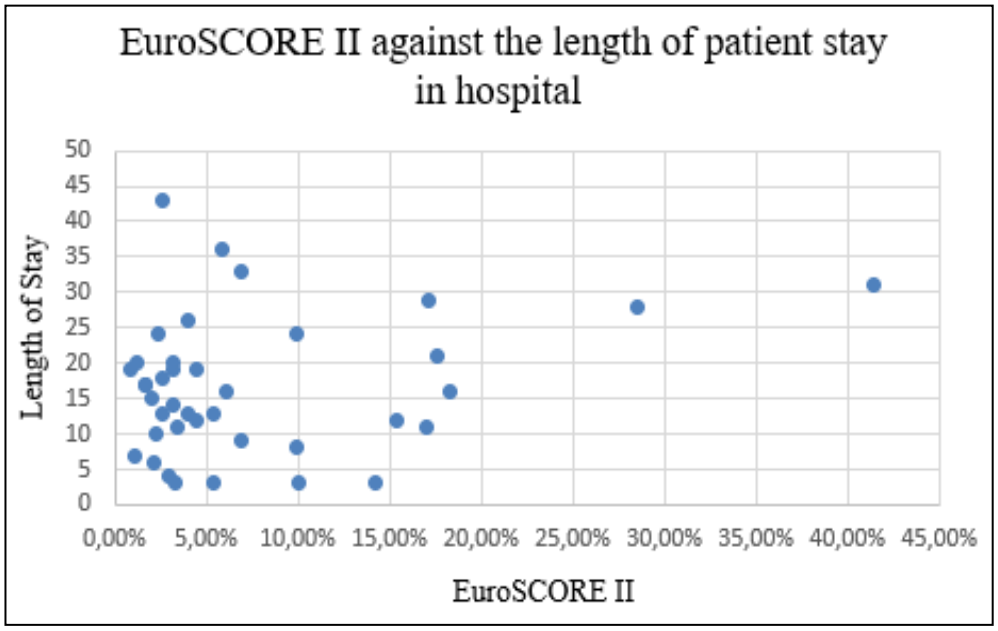

Figure 3. EuroSCORE II against the length of patient stay in hospital

The 3 graphs show a pattern-less figure, which indicated that EuroSCORE II cannot properly assess the duration of inotropic, vasopressors, and length of stay in hospital.

This study also assessed EuroSCORE II in predicting the risk of morbidity in CABG postoperative patients. The components of morbidity include blood transfusion, arrhythmia, renal failure, low cardiac output syndrome, and bleeding during surgery. Meanwhile, the results of EuroSCORE II on the morbidity component are shown in Table 3.

Studies showed that patients with higher EuroSCORE II need red blood cell transfusion (17). At Dr. Soetomo General Academic Hospital, the patient's demand for blood transfusion increases in response to an increase of EuroSCORE II. However, patients who did not need blood transfusions also have

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a higher EuroSCORE II than patients who only need 1-2 blood packs. This occurs because of a fairly wide sample variation, therefore, EuroSCORE II does not always accurately predict the need for blood transfusions.

Table 3. EuroSCORE II in assessing the risk of morbidity in CABG postoperative patients

Variable	Total (n=39)	EuroSCORE II Mena ± SD
Blood Transfusion		
1 pack	20	5,79% ± 6,31%
2 pack	6	7,79% ± 5,75%
3 pack	3	12,84% ± 8,84%
No	10	9,52% ± 12,44%
Renal Failure		
Yes	2	10,31% ± 9,71%
No	37	7,43% ± 8,42%
Low Cardiac Output Syndrome		
Yes	5	3,39% ± 1,53%
No	34	8,19% ± 8,8%
Bleeding Durante operation		
Yes	31	7,35% ± 8,97%
No	8	8,46% ± 5,84%
Arrhythmia		
Yes	8	7,25% ± 6,5%
No	31	7,66% ± 8,88%

EuroSCORE II is more accurate in predicting the risk of renal failure because one of its assessment components is renal function. In renal failure of patients, there is a higher average EuroSCORE II value (10.31%) compared to patients who did not suffer renal failure (7.43%). In Brazil, the risk of renal failure increases in line with an increase in EuroSCORE, with sensitivity and specificity at a score of 3.5% (18).

Moreover, EuroSCORE II with a score of 10% is a strong predictor of Low Cardiac Output Syndrome, with a value of 27.1% compared to 10.7%, p<0.0001 (13). In this study, EuroSCORE II was unable to predict the risk of low cardiac output syndrome in CABG postoperative patients. This is because patients with low cardiac output syndrome had a lower average EuroSCORE II value of 3.39% compared to those without low cardiac output syndrome (8.19%).

The risk of Durante-operative bleeding in CABG patients was not also assessed because EuroSCORE II has a poor discriminatory power in predicting major complications such as intraoperative stroke, stroke incidence in the first 24 hours, postoperative myocardial infarction, wound infection, gastrointestinal complications, and re-exploration for bleeding (16).

EuroSCORE II is also poor in discriminating the risk of arrhythmias because the patients had a lower mean of 7.25% compared to others without this condition namely 7.66%. The inaccuracy of EuroSCORE II in assessing the components of morbidity occurs because patients with each morbidity have an average value of EuroSCORE II lower than patients who do not suffer. Based on standard deviation, the overall morbidity components have a fairly wide sample variation, therefore, EuroSCORE II is not always accurate in assessing the overall risk of morbidity.

CONCLUSION

EuroSCORE II is inadequate to predict morbidity and mortality in postoperative patients, therefore, it is considered less effective.

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Original Article

CORRELATION OF IL-1β LEVEL AND BODY TEMPERATURE TO THE SEVERITY OF ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) AND MORTALITY IN COVID-19 PATIENTS

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ABSTRACT

Introduction: IL-1β and IL-6 are cytokines that have major roles in cytokine storms and endogenous pyrogens. Several studies have also displayed the effectiveness of IL-1β inhibitors in COVID-19 patients in minimizing severity and mortality. **Objective:** This study aims to analyze the correlation between IL-1β and body temperature with ARDS severity and mortality in COVID-19 patients. **Materials and Methods**: This is an analytical observational study with a prospective cohort design. A total of 54 patients have met the inclusion criteria from July to September 2020. This study mainly applied the Spearman-Rho, Mann Whitney, free sample T2 test, and Chi-Square test. **Results and Discussion**: The correlation between body temperature and IL-1β levels in COVID-19 patients with ARDS did not show a statistically significant difference towards mortality and ARDS severity, as shown by the *p*-value > 0.05 in the analysis tests of each of the variables studied. Nonetheless, the occurrence of ARDS (p = 0.022), the severity of ARDS (p = 0.001), application of mechanical ventilation (p = 0.00), secondary infection (p = 0.00), and length of stay (p = 0.042) were found to be statistically significant towards COVID-19 patients' mortality. **Conclusion**: Body temperature does not correlate with the occurrence of ARDS, the severity of ARDS, mortality, and IL-1β levels. IL-1β levels and transformation in IL-1β levels also do not correlate with mortality as well as the occurrence and severity of ARDS, but the use of mechanical ventilation, secondary infection, and length of stay were correlated with mortality in COVID-19 patients.

Keywords: ARDS; COVID-19; Fever; IL-1β; Mortality; Severity

ABSTRAK

Pendahuluan: IL-1β dan IL-6 merupakan sitokin yang berperan besar dalam badai sitokin dan pirogen endogen. Beberapa penelitian memperlihatkan efektivitas inhibitor IL-1β pada pasien COVID-19 dapat mengurangi keparahan dan kematian. **Tujuan:** Penelitian ini bertujuan untuk mempelajari hubungan kadar IL-1β dan suhu tubuh dengan tingkat keparahan ARDS dan mortalitas pada pasien dengan COVID-19. **Material dan Metode**: Penelitian ini merupakan studi observasional analitik dengan desain kohort prospektif. Sejumlah 54 pasien memenuhi kriteria inklusi dan eksklusi dari Juli sampai September 2020. Studi ini menggunakan uji analisis Spearman-Rho, Mann Whitney, uji T2 sampel bebas, dan Chi-Square. **Hasil dan Diskusi**: Hubungan suhu tubuh dan kadar IL-1β pada pasien COVID-19 dengan ARDS tidak memiliki kemaknaan secara statistik terhadap mortalitas dan keparahan ARDS. Hal ini terlihat dalam uji analisis pada setiap variabel yang diteliti dimana nilai p > 0,05. Meskipun begitu terjadi nya ARDS (p 0,022), tingkat keparahan ARDS (p 0,001), penggunaan ventilasi mekanik (p 0,00), infeksi sekunder (p 0,00) dan lama perawatan (p 0,042) secara statistik bermakna terhadap mortalitas pada pasien COVID-19. **Kesimpulan**: Suhu tubuh tidak berkorelasi terhadap terjadi nya ARDS, tingkat keparahan ARDS, mortalitas, dan kadar IL-1β. Kadar IL-1β dan perubahan kadar IL-1β tidak berkorealsi dengan mortalitas, kejadian dan tingkat keparahan ARDS; tetapi penggunaan ventilasi mekanik, infeksi sekunder dan lama perawatan berkorelasi dengan mortalitas pasien COVID-19.

Kata Kunci: ARDS; COVID-19; Demam; IL-1β; Mortalitas; *Severity*

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INTRODUCTION

At the end of December 2019, several patients in Wuhan China were hospitalized with an initial diagnosis of pneumonia whose cause was still unknown. The patients were linked to a fish market in Wuhan. Then, on February 11, 2020, the WHO determined that the cause of pneumonia cases in Wuhan was a new type of coronavirus, which was later named COVID-19, as it was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1).

A study of the risk factors associated with the incidence of Acute Respiratory Distress Syndrome (ARDS) and death in patients with COVID-19 stated that high fevers of above 39.0ºC were also associated with the incidence of ARDS. The study also suggested that fever was associated with better outcomes (2). The Infectious Disease Society of America defines a fever as a core body temperature of 38.3ºC or more. High temperatures can provide a protective mechanism effect because pathogens often show optimal replication at temperatures below 37.0ºC, therefore an increase in body temperature by the host can inhibit the reproduction of pathogens. In addition, increased body temperature is associated with increased innate immunity and is associated with microbial and viral destruction. However, temperatures of over 40.0ºC could increase mortality (3). A study showed that in the early stages of ARDS, specifically in the acute phase, fevers are associated with increased survival rates, but it is still unclear whether the beneficial effect of fevers is due to the adequate levels of acute-phase proteins or the fever itself (4).

The interaction between exogenous pyrogens (e.g., microorganisms) or endogenous pyrogens such as interleukin-6 (IL-6), IL-1, tumor necrosis factor (TNF)-α, with organum vasculum in the *lamina terminalis* (OVLT) causes fever production. This is a pro-inflammatory cytokine that is most relevant to the acute phase response process. The pro-inflammatory IL-1 is IL-1α and IL-1β, especially IL-1β (5). IL-1β is never produced by healthy individual cells. In addition to triggering fever in the hypothalamus, IL-1β is secreted by dead cells by the process of pyroptosis (6). Additionally, IL-1β and IL-6 are cytokines that are overproduced and cause hyper inflammation in COVID-19 (7). A 2020 study of cytokine levels in a COVID-19 case showed that IL-1β levels were higher in patients with COVID-19 than in healthy subjects and that it was also higher in COVID-19 patients that were admitted to the ICU than in those without ICU admission (8). Several studies have also shown the effectiveness of IL-1β inhibitors in COVID-19 patients to reduce severity and mortality (9,10).

Conversely, many studies have shown that the role of IL-1β as a pro-inflammatory cytokine in COVID-19 is not significant enough compared to IL-6 or TNF- (11–13). Therefore, this study aims to examine the relationship between IL-1β levels and body temperature with the severity of ARDS and mortality in patients with COVID-19 and whether fevers could provide better outcomes in these patients.

MATERIALS AND METHODS

This is an analytical observational study with a prospective cohort design. The study's population are COVID-19 patients who were treated in the Special Isolation Room of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The research samples were collected from the population according to several inclusion and exclusion criteria from July to September 2020. It was found that 55 patients met the inclusion criteria. However, 1

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patient dropped out due to sample errors, so this study used the data of 54 patients. The inclusion criteria in this study were adult patients (above 19 years), patients with clinical symptoms of COVID-19, have tested positive for COVID-19 and confirmed twice by RT-PCR results from nasopharyngeal swab tests, willingness to participate in the study, was receiving treatment according to standard protocol, and met the ARDS criteria based on the Berlin criteria. The exclusion criteria in this study were patients with HIV or other immunocompromised diseases, patients with a history of autoimmune disease or receiving immunosuppressant therapy, patients with malignancy, surgical or perioperative patients, patients who were pregnant, or was in the puerperium period.

Patients who met the inclusion criteria were recorded and a medical history check was conducted regarding the patients' history of fever and the first onset of symptoms. If they had a history of fever, the date of the patient's arrival to the hospital and the number of days of fever was recorded. A thorough physical examination was then performed, the core temperature was measured on arrival with a tympanic membrane thermometer, using infrared Braun Thermoscan 7 IRT 6520. Peripheral blood sampling for IL-1β examination was performed on arrival (H-0 treatment) and was repeated on the 6th day of treatment. The sample was then analyzed by using the CBA technique (Cytometric Bead Array). If there is a history of using antipyretic drugs, then the blood samples and temperature re-measurements were carried out at least 6 hours after the antipyretic drug administration. During treatment, core temperature was measured in the morning (basal temperature) according to the circadian cycle and repeated every shift (3 times a day). Temperature measurement was performed through the ear (tympanic membrane) by inserting a thermometer probe into the ear, making sure that the ear is not covered with cerumen. The otoscope maneuver was conducted, namely pulling the earlobe up and back until the entire ear canal is visible, then the entire thermometer probe is inserted into the ear canal in the direction of the corner of the eye until a sound is heard (5 seconds). The increase in body temperature between when the patient first arrived at the hospital and during treatment was recorded. The condition of secondary infection is evidenced by the examination of culture specimens.

The research was conducted from July 2020 until August 2021. Thus, this research was carried out for approximately one year. The research was conducted in the COVID-19 special treatment room at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, and the Clinical Pathology and Microbiology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

RESULTS AND DISCUSSION

A total of 55 people met the inclusion criteria in this study, but 1 patient was dropped out due to a sampling error. Therefore, the remaining 54 subjects were included in this entire study. In general, the subjects of this study have the characteristics listed in table 1.

Most of the subjects in this study were male patients (34 people or 63%), with an age range of 25 years to 73 years and a median age of 50.5 years. A total of 35 patients had comorbidities (64.8%), with the highest number of comorbidities being hypertension (31.5%) and Diabetes Mellitus (25.9%), obesity (13%), the remaining comorbidities were less than 10%. Most of the patients also had a history of fever before entering the hospital (41 people or 75.9%).

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Table 1. Demographics and Patient Characteristics.

Variable	N (%)	Median (*Range*)	*Mean* ± SD
Age (years)	54 (100%)	50.5 (25 – 73)	48.93 ± 11.535
Gender			
Male	34 (63%)	-	-
Female	20 (37%)		
Initial SOFA Score	54 (100%)	2.0 (0 – 3)	1.69 ± 0.609
The onset of Symptoms (days)	54 (100%)	7 (1 – 15)	7.13 ± 3.561
ARDS			
Have	37 (68.5%)	-	-
Not have	17 (31.5%)		
Comorbid			
Have	35 (64.8%)	-	-
Not have	19 (35.2%)		
Comorbid Type			
Hypertension	17 (31.5%)		
Diabetes Mellitus	14 (25.9%)		
Obesity	7 (13%)		
Asthma	1 (1.9%)	-	-
Coroner Heart Disease	1 (1.9%)		
COPD	1 (1.9%)		
CVA	1 (1.9%)		
Chronic Hepatitis B	1 (1.9%)		
HBsAg reactive	1 (1.9%)		
BMI (kg/m^2)	54 (100%)	25.71 (20.44 – 48.07)	26.56 ± 9.96
Highest temperature (ºC)	54 (100%)	38.15 (36.8 – 39.6)	38.29 ± 0.70
History of Fever			
Have	41 (75.9%)	-	-
Not Have	13 (24.1%)		
Secondary Infection			
Have	20 (37%)	-	-
Not Have	34 (63%)		
Use Mechanical Ventilation			
Have	12 (22.2%)	-	-
Not Have	42 (77.8%)		
Severity level of ARDS			
Mild	6 (11.1%)		
Moderate	21 (38.9%)	-	-
Severe	10 (18.5%)		
Mortality			
Death	10 (18.5%)	-	-
Live	44 (81.5%)		
Length of Stay (days)	54 (100%)	20 (8 – 69)	21.8 ± 13.10
IL-1β (pg/ml)	54 (100%)	2.48 (0.61 – 47.02)	6.49 ± 8.94

*In general, patients have more than 1 comorbidity. Categorical data uses percentages, numerical data uses median and mean ± SD.

The onset of symptoms varied from 1 day to 15 days with a median of 7 days, while the length of stay was 8 to 69 days with a median of 20 days. The Sequential Organ Failure Assessment (SOFA) score taken during the patients' arrival ranged from 0 to 3 with a median of 2. The patient with the lowest BMI recorded was at 20.44 kg/m2 and the highest was 48.7 kg/m2. The patient with the lowest temperature measured was at 36.8º C and the highest was 39.6º C. ARDS patients were categorized according to the Berlin criteria as mild, moderate, and severe. Most of the patients came with moderate severity of ARDS at 21 people (38.9%), followed by severe ARDS at 10 people (18.5%) and mild ARDS at 6 people (11.1%). The total number of ARDS patients was 37 people. The lowest IL-1β measurement obtained was 0.61 pg/ml and the highest was 47.02 pg/ml.

During treatment, 20 people (37%) had a secondary infection (secondary bacterial

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infection evidenced by culture results, bleeding, and blood clotting disorders), and other complications, of the 20 patients, 12 (22.2%) used mechanical ventilation, and 10 (18.5%) died. Furthermore, as many as 41 people (75.9%) had clinical symptoms of fever, followed by shortness of breath (68.5%), dry cough (59.3%), and the rest complained of runny noses, nausea, and vomiting, decreased appetite, cough with sputum, anosmia, diarrhea, sore throat, fatigue, abdominal pain, muscle pain, chest pain, headache, loss of consciousness, hemiparesis, and loss of sense of taste.

Table 2. Clinical Signs and Symptoms.

Clinical Symptoms	N (%)
Fever	41 (75.9%)
Shortness of breath	37 (68.5%)
Dry Cough	32 (59.3%)
Rhinorrhea	10 (18.5%)
Nausea and vomiting	7 (13%)
Decreasing of Appetite	7 (13%)
Cough with sputum	9 (16.7%)
Anosmia	6 (11.1%)
Diarrhea	4 (7.4%)
Sore Throat	6 (11.1%)
Fatigue	6 (11.1%)
Stomach ache	3 (5.6%)
Muscle pain	3 (5.6%)
Chest pain	2 (3.7%)
Headache	2 (3.7%)
Loss of consciousness	1 (1.9%)
Hemiparesis	1 (1.9%)
Loss of Taste	1 (1.9%)

* Generally, patients have more than 1 clinical symptom, the assessment was done when the patient arrived at the hospital

Table 3. Analysis of the Relationship between Body Temperature and IL-1β with ARDS

	ARDS	N (%)	Median (*Range*)	*Mean* ± SD	*p*
Body Temperature (°C)	Yes	37 (68.5%)	38.5 (37.0 – 39.6)	38.38 ± 0.67	0.146
	No	17 (31.5%)	38.0 (36.8 – 39.6)	38.08 ± 0.73	
IL-1β (pg/ml)	Yes	37 (68,5%)	2,64 (0,61 – 18,42)	5,12 ± 5,14	0,502
	No	17 (31,5%)	2,32 (1,61 – 47,02)	9,49 ± 13,83	

* Analysis using free sample T2 test, significant if p < 0.05

It was found that ARDS patients had a temperature range of 37.0°C to 39.6°C with a median of 38.5°C, while patients without ARDS had a temperature range of 36.8°C to 39.6°C, with a median of 38.0°C. By using the free sample T2 test, a *p*-value of 0.146 was obtained where the *p*-value of < 0.05 was statistically significant. Therefore, the relationship between body temperature and ARDS was not statistically significant.

Moreover, ARDS patients and those without ARDS did not have a significant difference in IL-1β levels. This can be seen from the median value of IL-1β in ARDS patients of 2.64 pg/ml with a range of 0.61 to 18.42 pg/ml and in patients without ARDS of 2.32 pg/ml with a range of 1.61 to 47.02 pg/ml. By using the Mann-Whitney comparison test, a *p*-value of 0.502 was obtained where the *p*-value of <0.05 was

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statistically significant. Therefore, the relationship between IL-1β and ARDS was not statistically significant. The IL-1β recording was conducted within the first 24 hours of treatment if the patient had ARDS on that day and at day 6 if there was ARDS between day 2 and day 6 of treatment.

A study with a retrospective cohort design in China was conducted with a sample of 201 patients with an age range of 21 to 83 years and found that the risk factors for ARDS in COVID-19 patients were old age (> 65 years) and high fever (> 39.0^{o}C). Comorbidities such as hypertension and DM, neutrophilia, lymphocytopenia, increased markers of organ failure (Aspartate Aminotransferase (AST), urea, Lactate dehydrogenase (LDH)), increased inflammatory markers (C-Reactive Protein (CRP), serum ferritin), increased coagulation function indicators (PT and D-Dimer) were also significantly associated with a high risk of developing ARDS. Whereas ARDS patients who experience death tend to be related to old age, other comorbidities such as hypertension, methylprednisolone treatment, use of mechanical ventilation, and use of ECMO. Interestingly, this study was stated that patients that had a high fever, although strongly associated with the risk of developing ARDS, were not associated with death (2).

Fever is common in critically ill patients, especially in patients with ALI/ARDS. ARDS is also a frequent complication of heatstroke. A study of the relationship between temperature and ARDS in experimental rats showed that the increase in ambient temperature indicates the condition of Febrile-Range Hyperthermia (FRH), a condition where an increase in core body temperature is equivalent to 2.0^{o}C can significantly increase the occurrence of ARDS. FRH greatly increases the accumulation of pulmonary PMN cells, endothelial dysfunction, and epithelial trauma. These are the three main signs of ARDS in humans. This study showed that FRH amplifies the expression of the chemokine CXC as the promoter of neutrophil cells. This study also emphasized that the FRH model used was not a regulated fever model, as the rapid increase in core body temperature was a result of the acute phase response. The increasing core body temperature in this study was achieved gradually and steadily and without pro-inflammatory signals or other components of the acute phase response (14).

As is known in the pathophysiology of ARDS, the occurrence of ARDS begins with an exudative phase characterized by damage to the alveolar endothelium, epithelial defenses, and accumulation of protein-rich fluid in the interstitium and alveoli mediated by innate immune cells. Macrophages that reside in the alveoli then secrete pro-inflammatory cytokines such as IL-6, IL-1β, TNF, IL-8, and other pro-inflammatory cytokines, which then result in the recruitment of neutrophils and monocytes or macrophages, as well as the activation of alveolar epithelial cells and other proinflammatory cells. T effector cells promote and sustain the inflammatory process and tissue trauma (15). The same pro-inflammatory cytokines also play a role in the mechanism of fever (TNF, IL-6, IL-1β). Therefore, body temperature does not directly cause ARDS or increase the risk of ARDS but it has the same pro-inflammatory cytokine mechanism as ARDS pathogenesis.

The wide standard deviation value may be caused by the wide jump of IL-1β values or other factors that can affect IL-1β levels and cannot be controlled in this study, such as heart failure, angina, low serum Ca^{2+} levels, and dyslipidemia (16).

An observational pilot study on the pro- and anti-inflammatory response to severe

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COVID-19 with ARDS was conducted with a single-center retrospective study method and involved 39 study subjects. They found that their subject's IL-1β levels were below the reference range in COVID-19 patients. In severe cases with ARDS, the levels of IL-6 and CRP massively increased. However, this study had several limitations as only patients with ARDS were found, so it could not compare between those with ARDS and those without ARDS (17).

Another study regarding the evaluation of alpha defensin, IL1Ra, and IL-18 levels in COVID-19 patients with macrophage activation syndrome (MAS) and ARDS involving 100 study subjects was conducted prospectively and found that alpha defensin levels, IL1Ra, and IL-18 levels in patients with COVID-19 were significantly higher in patients who had MAS and ARDS than patients who did not experience MAS and ARDS. The levels of alpha-defensins, IL1Ra, and IL-18 levels with or without MAS or ARDS were higher than the control group, where this control group consisted of 50 asymptomatic health workers with negative routine PCR tests. The IL1Ra levels and IL-18 levels were higher in patients who died. The limitation of this study was that the patients with MAS and ARDS were older and have more comorbidities (18). Moreover, TNF-, IL-1β, IL-6, and IL-8 levels were found to be elevated in bronchoalveolar lavage fluid (BALF) specimens in ARDS patients, not in blood (19).

IL-1Ra is an antagonist of IL-1 where the IL-1Ra protein can exert an inhibitory effect on IL-1α and IL-1β, but IL-1Ra is a natural inhibitor of IL-1β. However, the study by Kerget et al 2021, could not explain the relationship between IL-1β levels and ARDS in patients with COVID-19 (18).

In this study, a total number of 10 patients died, all of whom were patients with ARDS. The body temperature of ARDS patients who died ranged from 37.0ºC to 39.5ºC, with a median of 38.45ºC. The study used a free sample T2 test, the *p*-value of 0.792 was obtained, where $p < 0.05$ was statistically significant. Therefore, the relationship between body temperature and mortality in ARDS patients was not statistically significant. ARDS in patients was determined on the first day of hospitalization and day 6 of treatment. This was done to determine whether there were patients who experienced a change in condition on day 6, from no ARDS to ARDS, between day 2 to day 6 of treatment. The highest body temperature during treatment was used and the measurements were taken by using tympanic membrane temperature.

Table 4. Analysis of the Relationship between Body Temperature and IL-1β with Mortality in Patients ARDS

		ARDS	N (%)	Median (*Range*)	*Mean* ± SD	*p*
Body Temperature (º C)	Yes					
		Non-Survivor	10 (27%)	38.45 (37.00 - 39.50)	38.34 ± 0.80	0.792
		Survivor	27 (73%)	38.50 (37.20 – 39.60)	38.40 ± 0.63	
	No					
		Non-Survivor	0 (0%)	0	0	
		Survivor	17 (100%)	38.00 (36.80 – 39.60)	38.08 ± 0.73	
IL-1β (pg/ml)	Yes					
		Non-Survivor	10 (27.02%)	2.07 (1.61 – 12.14)	3.28 ± 3.18	0.441
		Survivor	27 (72.97%)	3.63 (0.61 – 18.42)	5.79 ± 5.60	

* Analysis using free sample T2 test, significant if p < 0.05.

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No significant difference in IL-1β levels was found in patients who died and survived, with the median value of IL-1β in patients who died 2.07 pg/ml and ranged from 1.61 to 12.14 pg/ml, while in surviving patients the median was 3.63 pg/ml with a range of 0.61 to 18.42 pg/ml. By using the Mann-Whitney comparison test, a *p*-value of 0.441 was obtained where the *p*-value < 0.05 was statistically significant. Thus, the association of IL-1β with mortality in ARDS patients was not statistically significant. The IL-1β recording was conducted in the first 24 hours of treatment if the patient had ARDS on arrival and day 6 if there was ARDS between day 2 and day 6 of treatment.

A study of fever in the ICU as a predictor of mortality in mechanically ventilated COVID-19 patients was performed using a retrospective cohort method involving 103 patients. The results showed that patients who died had higher peak temperatures during their ICU stay compared to patients who survived. Patients whose highest temperature reached 39.5^{o}C had a 60% higher risk of death and the patients with a temperature reaching 40.0^{o}C had a 75% higher risk of death. Patients who experienced fever and were treated to achieve normothermia did not have different outcomes compared to patients who did not receive active therapy to achieve normothermia. Another aspect that was listed in this study was that in patients aged over 65 years, the male sex and patients with acidosis at the start of treatment had a higher mortality rate. Nevertheless, this study had several limitations because it was a retrospective study and there was no uniformity in the method of temperature measurement and temperature management (20).

Fever in COVID-19 begins 1 day after the symptom onset and can last up to 12 days in living patients, and 13 days in patients who die (21). A study regarding the risk factors for ARDS in COVID-19 patients was conducted with a retrospective cohort design in China. The sample was 201 patients with ages from 21 to 83 years and showed that although high fever (>39.0^{o}C) was strongly associated with the risk of developing ARDS, it was not related to the occurrence of death. As many as 73% of ARDS patients who survived had high fever > 39.0^{o}C, while only 41.2% of ARDS patients who died had high fever > 39.0^{o}C (2). ARDS is one of the main complications of COVID-19 that causes death.

A review of the febrile cycle as a potential mechanism to protect the respiratory system in COVID-19 patients stated that a low-grade fever (<38.0^{o}C) due to infection will stimulate a heat shock response (HSR) and lead to the accumulation of heat shock protein (HSP). Among them is HSP70 which belongs to the chaperone family, which has a protective effect and is known to be more effective in young adults than in old age. Using rats with adenovirus to stimulate the formation of HSP70, it was found that HSP70 can effectively protect against sepsis-induced ARDS by limiting the accumulation of neutrophils in the lung. Fever temperature longer than 2 to 3 hours will not cause an increase in the accumulation of heat-shock protein, it will cause degradation and ineffectiveness and cannot prevent apoptosis. Therefore, it is necessary to immediately maintain the body's temperature for several hours at normal temperature conditions (37.0^{o}C) to restore the effectiveness and ability of cells to produce HSP70 again (22).

A previous study on the inflammatory profile associated with higher mortality in COVID-19 patients that involved 41 patients prospectively showed that plasma IL-1Ra levels and IL-8 levels had a positive correlation with mortality in COVID-19

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ARDS patients. However, this study still requires further research (23).

Another study of IL-1β blockade with canakinumab in COVID-19 patients involved 88 patients in a prospective observational cohort design and showed an improvement in the PaO2/FiO2 ratio in 45 patients from the baseline with a median of 160 to 237 on day 7 of canakinumab therapy. Canakinumab is a monoclonal IgG antibody that specifically targets IL-1β. This study's result was a *p*-value < 0.0001, thereby indicating that this form of therapy reduces mortality. The drawbacks of this study were the small sample size and limited follow-up for 1 month. Moreover, the patients in this study also received other therapies such as tocilizumab, hydroxychloroquine, and steroids. Steroids in particular was one of the confounding factors. (9).

Table 5. Analysis of the relationship between body temperature and IL-1β with the severity of ARDS

	Severity Level	N (%)	Median (*Range*)	*Mean* ± SD	*p*
Body Temperature (°C)	Mild	6 (16.22%)	38.05 (37.70 – 38.80)	38.20 ± 0.48	0.05
	Moderate	21 (56.76%)	38.50 (37.00 – 39.50)	38.34 ± 0.76	
	Severe	10 (27.02%)	38.75 (37.8 – 39.6)	38.60 ± 0.57	
IL-1β (pg/ml)	Mild	6 (16.22%)	3.30 (0.61 – 15.92)	5.14 ± 5.58	0.301
	Moderate	21 (56.76%)	2.81 (1.26 – 18.42)	5.87 ± 5.75	
	Severe	10 (27.02%)	2.05 (1.50 – 12.14)	3.52 ± 3.30	

* Analysis using Spearman-Rho correlation test, it is significant if p < 0.05.

The temperatures of patients with mild ARDS were in the range of 37.7°C to 38.8°C with a median of 38.05°C. The body temperature of patients with moderate ARDS was 37.0°C to 39.5°C, with a median of 38.5°C, and the body temperature of patients with severe ARDS was 37.8°C to 39.6°C, with a median of 38.75°C. By using the Spearman-Rho correlation test, a *p*-value of 0.05 was obtained, where a *p*-value <0.05 was statistically significant. Therefore, the relationship between body temperature and the severity of ARDS was not statistically significant. The body temperature used was the highest body temperature recorded during treatment by the tympanic membrane temperature.

Furthermore, the levels of IL-1β at each level of ARDS severity also showed no significant difference. The median value of IL-1β in patients with mild ARDS was 3.30 pg/ml with a range of 0.61 to 15.92 pg/ml. Moderate ARDS patients had a median IL-1β value of 2.81 pg/ml with a range of 1.26 to 18.42 pg/ml. And patients with severe ARDS had a median of 2.05 pg/ml with a range of 1.50 to 12.14 pg/ml. By using the Spearman Rho correlation test, a *p*-value of 0.301 was obtained where the *p*-value <0.05 was statistically significant. Therefore, the relationship between IL-1β with the severity of ARDS was not statistically significant. The IL-1β levels were recorded in the first 24 hours of treatment if the patient had ARDS on that day and also at day 6.

A 2015 study of body temperature and mortality in patients with ARDS showed that in the early phase of ARDS, fever was associated with increased survival. For every 1.0°C increase in baseline temperature, mortality will decrease by 15%. This study used secondary analysis of body temperature by using data from the National Heart, Lung and Blood Institute and the ARDS network Fluid and Catheter Treatment Trial. The measurement of body temperature was done

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through the rectal, tympanic, and axillary temperatures of adult patients who meet the ARDS criteria based on the Berlin criteria for 48 hours or less. Mortality was based on 90 days of observation during treatment. However, this study has some limitations, there was a lack of standardized body temperature measurement methods and a lack of information or data on unit-based protocols for treating hypothermia and fever, which can vary widely (4). However, this study did not analyze the severity of ARDS.

Table 6. Analysis of Changes in IL-1β on Mortality in ARDS Patients

ARDS	N (%)	*p*
Non-Survivor		
Increasing ΔIL-1β	2 (20%)	
Decreasing ΔIL-1β	8 (80%)	
Survivor		
Increasing ΔIL-1β	12 (44.4%)	0.260
Decreasing ΔIL-1β	15 (55.6%)	
No ARDS	**N (%)**	
Survivor		
Increasing ΔIL-1β	8 (47.1%)	
Decreasing ΔIL-1β	9 (52.9%)	

*Analysis using Chi-Square Test, it means if p < 0.05; the difference in IL-1β levels on day zero and day 6

A study on the inflammatory profile associated with higher mortality in COVID-19 patients that involved 41 patients prospectively, showed that plasma IL-1Ra levels and IL-8 levels had a positive correlation with mortality in COVID-19 ARDS patients. However, this study still requires further research (23).The total number of ARDS patients was 37 people, 10 people died, and among the 10 people who died there were 2 people (20%) who experienced an increase in IL-1β and 8 people (80%) who experienced a decrease in IL-1β. There were 27 surviving ARDS patients, of which 12 people (44.4%) had an increase in IL-1β and 15 people (55.6%) experienced a decrease in IL-1β. There were no deaths found in patients who did not have ARDS (17 people). Of these 17 people, 8 people (47.1%) had an increase in IL-1β, and 9 people (52.9%) had a decrease in IL-1β. By using the Chi-Square test, a *p*-value of 0.260 was obtained, where the p-value <0.05 was statistically significant. Therefore, changes in IL-1β levels on mortality in ARDS patients were not statistically significant, so it cannot be concluded whether ARDS patients who survived or died have decreased, increased, or persistent IL-1β levels. The value of IL-1β was obtained from the difference in levels of IL-1β recorded on the first 24 hours of treatment and day 6 of treatment.

A 1995 study of inflammatory cytokines in BAL from ARDS patients, regarding persistent elevations, predicted poor outcomes. The study only showed that in patients who died, the levels of TNF- α, IL-1β, IL-6, and IL-8 were higher on the first day of ARDS than in the living group and increased persistently during treatment, where BAL and plasma samples were taken on the day of treatment. During day 1 and every 7 days after treatment, the results indicated a continuous injury process. This study was conducted prospectively and involved 27 consecutive patients with ARDS (24).

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Table 7. Analysis of the relationship between body temperature and IL-1β in patients with ARDS

ARDS	N (%)	*p*
Yes	37 (68.51%)	0.161
No	17 (25.92%)	0.310

* Analysis using Spearman-Rho correlation test, it is significant if p < 0.05.

The effect of body temperature on IL-1β in ARDS patients have a p-value of 0.161, while patients without ARDS has a *p*-value of 0.310. This analysis used the Spearman Rho correlation test, where the *p*-value < 0.05 was statistically significant. Therefore, this suggests that the relationship between body temperature and IL-1β in ARDS patients was not statistically significant. The highest temperature recorded was used during the first 6 days of treatment and IL-1β levels were recorded in the first 24 hours of treatment if the patient had ARDS on that day and day 6 if they had ARDS between day 2 and day 6 of treatment. There was no other study about the relationship between body temperature and IL-1β in patients with ARDS in COVID-19 yet.

No statistically significant analysis results were found for each of the specific objectives of this study. Thus, an analysis of patient characteristics on mortality was conducted to determine the variables of patient characteristics that were correlated with mortality.

Table 8. Analysis of Characteristics of Mortality

Variable		Death Frequency N (%)	Live Frequency N (%)	Median (*Range*)	*Mean* ± SD	*p*
Gender						
	Female	4 (40%)	16 (36.4%)			1.00*
	Male	6 (60%)	28 (63.6%)			
ARDS						
	No	0 (0%)	17 (38.6%)			**0.022***
	Yes	10 (100%)	27 (61.4%)			
Age(year)						
	Non-Survivor	10 (18.5%)	-	52 (40 – 73)	53.7 ± 11.43	0.149**
	Survivor	-	44 (81.5%)	50 (25 – 68)	47.8 ± 11.4	
Comorbid						
	Have	8 (80%)	27 (61.4%)			0.465*
	Not Have	2 (20%)	17 (38.6%)			
Fever History						
	Have	8 (80%)	33 (75.0%)			1.00*
	Not Have	2 (20%)	11 (25.0%)			
Comorbidity Type						
	Hypertension					
	Diabetes Mellitus	5 (50%)	12 (27.3%)			0.257*
	Obesity	4 (40%)	10 (22.7%)			0.424*
	Asma	0 (0%)	1 (2.3%)			1.00*
	Coroner Heart	2 (20%)	5 (11.4%)			0.601*
Disease		0 (0%)	1 (2.3%)			1.00*
	COPD	0 (0%)	1 (2.3%)			1.00*
	CVA	1 (10%)	0 (0%)			0.185*
	Chronic Hepatitis B	1 (10%)	0 (0%)			0.185*
	HBsAg reactive	0 (0%)	1 (2.3%)			1.00*

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Variable	Death Frequency N (%)	Live Frequency N (%)	Median (*Range*)	*Mean* ± SD	*p*
Clinical Symptom					
Fever	8 (80%)	33 (75.0%)			1.00*
Shortness of breath	7 (70%)	25 (56.8%)			0.501*
Dry Cough	8 (80%)	29 (65.9%)			0.476*
Rhinorrhea	1 (10%)	5 (11.4%)			1.00*
Nausea and vomiting	2 (20%)	5 (11.4%)			0.601*
Decreasing of Appetite	2 (20%)	4 (9.1%)			0.306*
Cough with sputum	1 (10%)	2 (4.5%)			0.466*
Anosmia	1 (10%)	8 (18.2%)			1.00*
Diarrhea	2 (20%)	8 (18.2%)			1.00*
Sore Throat	0 (0%)	7 (15.9%)			0.325*
Fatigue	0 (0%)	4 (9.1%)			1.00*
Stomachache	0 (0%)	1 (2.3%)			1.00*
Muscle pain	0 (0%)	2 (4.5%)			1.00*
Chest pain	0 (0%)	3 (6.8%)			1.00*
Headache	0 (0%)	6 (13.6%)			0.580*
Loss of consciousness	1 (10%)	1 (2.3%)			0.339*
Hemiparesis	0 (0%)	1 (2.3%)			1.00*
Loss of Taste	1 (10%)	0 (0%)			0.185*
Secondary Infection					
Have	9(90%)	11 (25.0%)			**0.00***
Not Have	1 (10%)	33 (75.0%)			
Use Mechanical Ventilation					
Yes	8 (80%)	4 (9.1%)			**0.00***
No	2 (20%)	40 (90.9%)			
Severity level of ARDS					
Mild	0 (0%)	6 (13.6%)			**0.001***
Moderate	4 (40%)	17 (38.6%)			
Severe	6 (60%)	4 (9.1%)			
Length of Stay (Days)					
Non-Survivor	10 (18.5%)	-	12.5 (11 – 25)	15.2 ± 4.98	**0.042*****
Survivor	-	44 (81.5%)	21 (8 – 69)	23.3 ± 13.9	
Onset of Symptom (Days)					
Non-Survivor	10 (18.5%)	-	8.5 (1 – 14))	8.0 ± 4.4	0.380***
Survivor	-	44 (81.5%)	7.0 (1 – 15)	6.93 ± 3.3	
qSOFA					
Non-Survivor	10 (18.5%)	-	2 (1 – 3)	1.7 ± 0.67	0.949***
Survivor	-	44 (81.5%)	2 (0 – 3)	1.68 ± 0.60	
BMI (kg/m^2)					
Non-Survivor	10 (18.5%)	-	25.74 (21.48 - 48.07)	28.44 ± 8.27	0.722***
Survivor	-	44 (81.5%)	25.34 (20.44 – 39.54)	26.14 ± 3.87	

* Chi-Square test, significant if p < 0.05; ** T-test, significant if p < 0.05; *** Mann-Whitney test, significant if p < 0.05.

In this study, analysis of the patients' characteristics on mortality showed that several factors that had statistical significance. The factors are ARDS conditions with a *p*-value of 0.022 using the Chi-Square test, secondary infection involvement with a *p*-value of 0.00 using the Chi-Square test, patients using ventilation mechanics with a *p*-value of 0.00 using the Chi-Square test, the severity of ARDS with a *p*-value of 0.001 using the Chi-Square test, and the length of stay period with a *p*-value of 0.042 using the Mann-Whitney test. All *p*-values in the analysis test were stated to be statistically significant if <0.05. These results showed that patients with ARDS are correlated with mortality with a *p*-value of 0.022, the presence of secondary infection during the treatment period also correlated with mortality with a *p*-value of 0.00, patients using mechanical

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ventilation correlated with mortality with a *p*-value of 0.00, ARDS severity also correlated with mortality with a *p*-value of 0.001. All results were obtained from conducting the Chi-Square test. Another variable that correlates with mortality is the length of stay. By using the Mann-Whitney test, a *p*-value of 0.042 was obtained with a median value of 12.5 days and a range of 11 to 25 days and a mean ± SD of 15.2 ± 4.98 in patients who died.

These results showed that patients with ARDS, the presence of secondary infection during the treatment period where the secondary infection was proven by specimen culture, patients using mechanical ventilation, and the severity of ARDS, all correlate with mortality.

Secondary infections generally come from secondary bacterial lung infections, followed by the blood and urinary tract. All patients who used mechanical ventilation were at severe to critical severity of COVID-19 when they arrived at the hospital and on average had a severe degree of ARDS. This shows that patients with ARDS, patients with ARDS with extreme severity, secondary infections, and patients that used mechanical ventilation, all have an association with mortality. Another variable that correlates with mortality is the length of treatment. The results suggest that the longer the treatment, the greater patient's survival.

Research on mortality in COVID-19 patients with ARDS and the use of corticosteroids has shown that patients with ARDS have high mortality and require appropriate and aggressive therapy. This study is a meta-analysis, which found that the mortality with the highest ARDS is in China, especially at the beginning of the pandemic, at 69%. In Europe, the countries with the highest ARDS mortality are Poland at 73%, followed by Spain at 40%, and France at 19%, with Germany having the lowest mortality. Globally, the total mortality in COVID-19 patients with ARDS is 39% with or without corticosteroid therapy. This study involved 28 articles that were screened and matched the inclusion and exclusion criteria (25).

Another study of COVID-19 patients with secondary infection showed that the risk of secondary infection increased after receiving invasive mechanical ventilation and intravenous devices, which in turn increased mortality. This study was a retrospective multi-center cohort study and involved 612 patients. Secondary infection was evidenced by clinical symptoms, supportive radiological results, and specimen culture results. Most of the bacteria that were causes of respiratory tract infections were Gram-negative bacteria (26).

Another meta-analysis study of the case fatality rate (CFR) in COVID-19 patients using mechanical ventilation, stated that the overall CFR in patients that used mechanical ventilation reached 45%. Nearly half of the patients that received mechanical ventilation died. The reported CFR was higher in older patients, and was higher at the onset of the pandemic, possibly due to limited ICU resources. This study involved 69 articles after being screened to be according to the inclusion and exclusion criteria (27).

CONCLUSION

From this study, it can be concluded that body temperature does not correlate with the occurrence of ARDS, the severity of ARDS, as well as mortality, and IL-1β levels. IL-1β levels and transformation in IL-1β levels did not correlate with mortality and the occurrence and severity of ARDS.

The use of mechanical ventilation, secondary infection, and length of stay were

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correlated with mortality in COVID-19 patients. Further studies are needed with serial IL-1β samples that are taken more frequently during treatment, along with other pro-inflammatory cytokines.

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Case report

SUCCESSFUL ANESTHETIC MANAGEMENT FROM SEPARATION SURGERY OF PYGOPAGUS CONJOINED TWIN; LESSON-LEARNING WITH A TELEANESTHESIA

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ABSTRACT

Introduction: The management of conjoined twins requires multidisciplinary teamwork. The complex problems in conjoined twin separation surgery are challenging for anesthesiologists without experience in the management of conjoined twins. **Objective:** To describe anesthetic management and utilization of teleanesthesia in conjoined twin separation surgery. **Case Report**: Sixty days-old pygopagus type conjoined twins, with a total body weight of 7030 grams. Both babies looked healthy, moved actively, found no respiratory function disorders, were hemodynamically stable and had no congenital abnormalities. The sacral region's computerized tomography scan (CT-scan) reveals conjoined twins with skin unification and subcutaneous in the perianal region and no internal-vertebral-spinal fusion. Two anesthesia teams performed the management of anesthesia. After confirming there was no cross-circulation with the atropine test, we alternately induced anesthesia by inhalation technique while maintaining spontaneous breathing. Anesthesia was maintained with sevoflurane 2.0-3.0 vol%, in a mixture of oxygen and air with a flow of 4 L/min using Jackson Reese. Circulating volume, hemodynamic stability, and normothermia were maintained intraoperatively. The separation surgery lasted 20 minutes, and the total surgical time for each baby was two hours. Awake extubation was performed immediately after the surgery was complete. Both babies underwent postoperative care at the PICU and were discharged on day 11. During the pre-operative for surgery, the local team conducted telemedicine consultations with the pediatric anesthesia team at Dr. Soetomo hospital and performed intra-anesthesia telementoring. **Conclusion:** Careful preparation and pre-operative evaluation, proper intra-anesthesia maintenance and monitoring, as well as good communication and teamwork, are keys to successful anesthesia management in conjoined twin separation surgery. Consultation and assistance from an experienced team during surgery using teleanesthesia are significantly beneficial to the anesthesiologist without experience in conjoined twin separation surgery.

Keywords: Conjoined Twin; Childbirth Complications; Pygopagus; Telemedicine, Teleanesthesia

ABSTRAK

Pendahuluan: Penanganan bayi kembar siam memerlukan kerjasama tim dari berbagai multidisiplin. Kompleksitas permasalahan yang dapat terjadi, menjadi tantangan besar bagi ahli anestesi yang belum berpengalaman dalam menangani operasi pemisahan kembar siam. **Tujuan:** Untuk memaparkan manajemen anestesi dan pemanfaatan tele-anestesi pada operasi pemisahan kembar siam. **Kasus:** Bayi perempuan kembar siam tipe pygopagus, berumur 60 hari dengan berat badan total 7030 gram. Bayi lahir dengan persalinan spontan pervaginam, usia aterm, dengan berat lahir total 4.000 gram. Kedua bayi tampak sehat, bergerak aktif, tidak ditemukan gangguan fungsi respirasi, hemodinamik stabil, dan tanpa kelainan kongenital penyerta. Pemeriksaan *computerized tomography-scan* (CT-scan) daerah sacral menunjukkan bayi kembar siam dengan penyatuan kutis dan subkutis di regio perianal serta tidak tampak penyatuan organ internal-vertebral-spinal. Manajemen anestesi dilakukan oleh dua tim anestesi. Setelah memastikan tidak terdapat sirkulasi silang dengan uji sulfas atropine, induksi anestesi dilakukan secara bergantian dengan teknik inhalasi dengan mempertahankan pernapasan spontan. Pemeliharaan anestesi dengan sevoflurane 2,0 – 3,0 vol%, dengan flow 4 L/menit dalam campuran oksigen dan udara menggunakan Jackson Reese. Volume sirkulasi, stabilitas hemodinamik, dan normotermi dipertahankan selama intraoperasi. Operasi pemisahan berlangsung selama 20 menit, dan total waktu pembedahan pada masing-masing bayi selama dua jam. Ekstubasi sadar segera dilakukan setelah pembedahan selesai.

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Pascaoperasi, pasien menjalani perawatan di PICU dan dipulangkan pada hari ke 11. Selama persiapan preoperative hingga tindakan pembedahan, tim anestesi setempat melakukan konsultasi ke tim anestesi pediatri RSUD dr Soetomo secara telemedicine dan telementoring intra-anestesi. **Kesimpulan:** Persiapan dan evaluasi praoperasi yang cermat, pemeliharaan intraanestesi yang tepat, serta komunikasi dan kerjasama tim yang baik merupakan kunci sukses manajemen anestesi pada operasi pemisahan bayi kembar siam. Konsultasi dan pendampingan secara tele-anesthesia memberikan manfaat yang besar bagi tim anestesi yang belum berpengalaman dalam operasi pemisahan bayi kembar siam.

Kata kunci: Kembar Siam; Komplikasi Bayi Baru Lahir; *Pygopagus; Telemedicine; Tele-anesthesia*

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INTRODUCTION

Conjoined twin is a rare congenital disorder in humans and becomes one of the most difficult to manage. This disorder requires medical and psychological attention and is an example of medicine's most complex problem-organizing and ethical issues (1). The incidence of conjoined twins is 1.47: 100,000 live births (2). Based on the fusion, both dorsal and ventral, conjoined twins can be divided into eight subtypes: omphalopagus, thoracopagus, cephalopagus, ischiopagus, parapagus, craniopagus, rachipagus and pygopagus. Thoracopagus is the most common type (40%), followed by omphalopagus (32%), pygopagus (19%), ischiopagus (6%), and craniopagus (2%) (3).

The management of conjoined twins requires good teamwork by involving various multidisciplinary. Well-organized planning and management, both in anesthesia and surgery, are crucial to obtain a good outcome. Besides the medical aspect, careful ethical and moral considerations involving families, psychologists, religious leaders, and legal experts must also be considered. Publication of the management of conjoined twins to the media also needs to be communicated carefully. Therefore media coverage becomes a constructive potential to increase understanding of conjoined twins in society, mobilize community roles, and increase team spirit instead of becoming a burden (1).

Anesthetic management for conjoined twin separation surgery is an enormous challenge for pediatric anesthesiologists. It should be emphasized that each conjoined twin should be treated as a separate entity with specific problems from each baby; thus, it requires two anesthesia teams for the separation surgery (1,2).

In a health facility performing conjoined twin separation surgery for the first time, an experienced pediatric anesthesia team or a local team with direct assistance from an expert team should handle the anesthetic management. The absence of an experienced pediatric anesthesia team poses an extra challenge for an anesthesiologist without experience in conjoined twin separation surgery. Consultation on the anesthetic management of conjoined twins and intra-anesthesia assistance of an experienced team using telemedicine can solve this problem.

Here, we describe the success of anesthetic management in pygopagus conjoined twin separation surgery performed by an anesthesiologist team without experience in separation surgery. The surgery was performed with remote assistance by an expert anesthesiologist using teleanesthesia. Apart from that, this article describes other

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aspects to consider during the management of conjoined twins.

CASE REPORT

We have obtained written consent from both patients' parents to be included in this report. This conjoined twin separation surgery was the first case performed at Ulin hospital, Banjarmasin. When we received the referral of conjoined twins in our hospital, we immediately formed a multidisciplinary team of 52 people with a pediatrician as the chairperson. This conjoined twins' team regularly met to discuss the management of the conjoined twins.

The twin baby girl with Pygopagus conjoined was born by spontaneous delivery, term, with a total birth weight of 4,000 grams (Figure 1). Both babies looked healthy, moved actively, had no respiratory function disorders, were hemodynamically stable, and had no congenital abnormalities. The laboratory test results were within normal ranges (Table 1). At seven days, a computerized tomography scan (CT scan) of the sacral region showed conjoined twins with skin and subcutaneous unification in the perianal region. It did not reveal the internal-vertebral-spinal organ's unification (Figure 2). Echocardiographic examination obtained normal heart function. These babies underwent treatment in the NICU until the separation surgery was performed.

Since the fusion was limited to the skin and subcutaneous tissue, which required simple surgery, the team decided that our hospital surgical team performed the separation surgery of the conjoined twins without direct assistance from an experienced team. In addition, a spike in daily cases of COVID-19 in Indonesia at the time of the surgery resulted in travel restrictions that made it impossible for an expert team to attend. However, considering the complexity of anesthetic management of conjoined twin separation surgery, we conducted telemedicine consultation and intra-anesthesia remote assistance with the pediatric anesthesiologist team from Dr. Soetomo General Academic Hospital, Surabaya, which has experience managing conjoined twins.

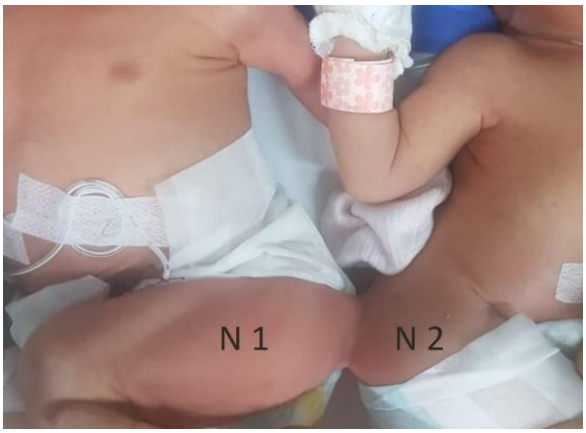

Figure 1. Pygopagus Conjoined Twins. There was Unification in The Pelvic Area. N1 Babies Had A Larger Body Size Than N2 Babies

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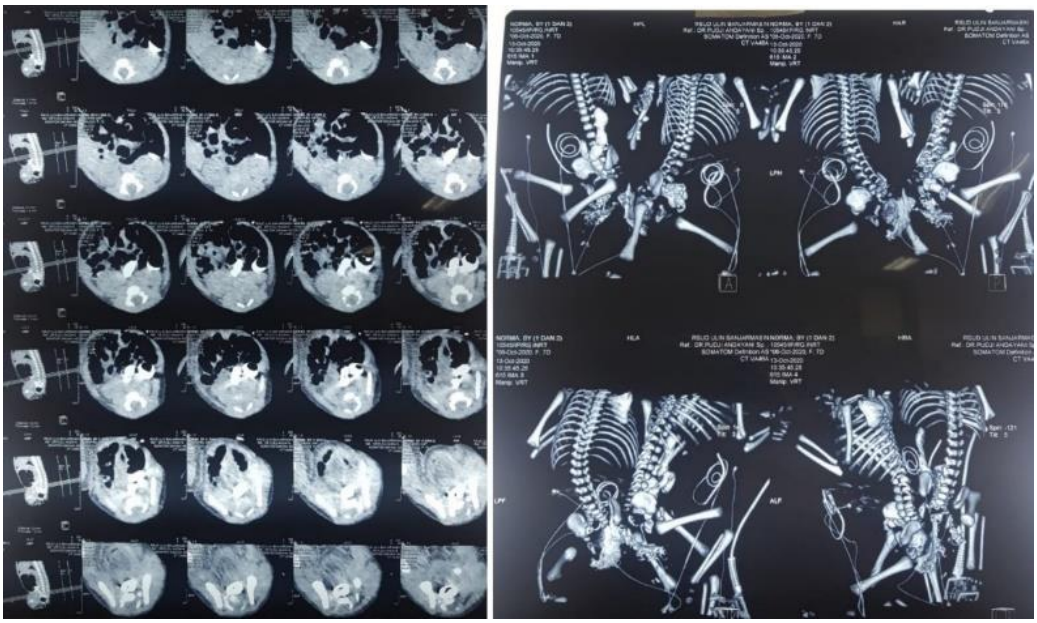

Figure 2. Computerized Tomography-scan (CT-scan) of the sacral region at 7 days of age. It showed conjoined twins with skin and subcutaneous fusion in the perianal area and no visible internal-vertebral-spinal fusion.

Table 1. The Summary of Laboratory Findings.

Laboratory parameters	N1			N2		
	Day 2	Preop	Postop	Day 2	Preop	Postop
Hemoglobin (g/dL)	14.1	15.8	14.5	13.8	15.8	14.6
Hematocrit (%)	42.2	45.7	42.4	39.3	46.3	42.3
White blood count (/µL)	15,300	8,700	7,900	14,100	10,500	7,400
Platelet count (/µL)	271,000	368,000	383,000	336,000	388,000	366.000
SGOT (U/L)	48	24	32	49	27	35
SGPT (U/L)	19	27	28	24	13	26
Ureum (mg/dL)	25	30	29	28	37	25
Creatinin (mg/dL)	0.45	0.18	0.25	0.52	0.24	0.21
Blood glucose (mg/dL)	132	126	123	73	132	122
Albumin (g/dL)		3.9	4.0		4.0	3.7
PT/APTT (second)		10.3/34.6	13.1/39.2		10.9/34.6	11.8/34.3
Na/K/Cl (Meq/L)		137/5.3/113	138/4.6/109		137/5.9/114	138/4.9/110

Before surgery day, we performed two consecutive days of surgery simulations in operating rooms using dolls and involved the entire team in charge (Figure 3). The surgery was performed in two adjacent operating. The first operating room was equipped with two anesthesia machines, two patient monitors, and other anesthesia equipment was doubled. Two anesthesia teams, each comprising one anesthesiologist consultant, carried anesthetic management out.

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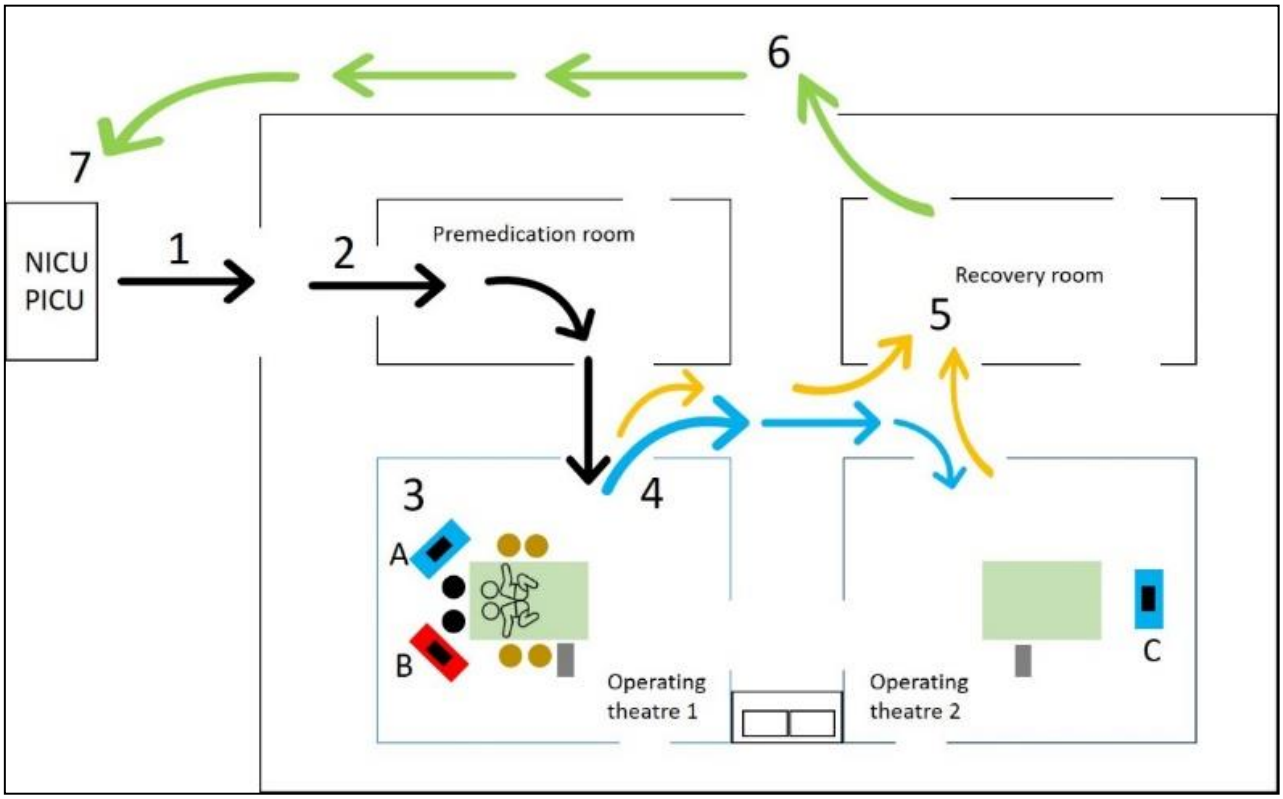

Figure 3. Simulations of A Conjoined twin's Separation Surgery in The Operating Room. The order of procedure, division of tasks, and roles of each team have been determined. Team 1 (pediatricians and infant nurses) is assigned to transfer babies to the operating room, then received by team 2 (anesthesia resident and nurses). The babies are then transferred to the premedication room and operating room 1 (black arrow). The two anesthetic teams responsible for each baby were ready to receive conjoined twins (3). After a successful separation surgery, team 4 (anesthesia resident, nurses, and surgical resident) will transfer N2 babies into the second operating room (blue arrow). The second surgical and anesthesia team has been prepared to receive N2 babies. After the surgery is completed, both babies are transferred to the recovery room by the anesthesia team (yellow arrows) and received by team 5 (anesthesiologist and nurses). Team 6 (pediatrician and infant nurse), together with the anesthesia team of each baby, make a transfer from the recovery room to the PICU (green arrow) and will be received by Team 7 (pediatrician, pediatric resident, infant nurse) in the PICU.
Notes: A; Anesthesia machine, patient monitor, and workstation for infants N2. B; Anesthesia machine, patient monitor, and workstation for babies N1; Anesthesia machine, patient monitor, and workstation for infant N2 in operating room two after separation. Black circle; anesthesiologist position. Brown circle; the position of the surgical team during surgery. Gray square; surgical instrumentation table.

We performed the separation surgery when the baby was 60 days old, with a total body weight of 7030 grams. To avoid confusion, we named the two babies N1 (the bigger baby) and N2. As per the elective surgery protocol in our hospital during the COVID-19 pandemic, two days before surgery, both babies underwent RT-PCR tests, and the results were negative for SARS-CoV-2 for both babies. Both babies had peripheral venous access using a large-bore cannula, and a peripherally inserted central catheter (PICC) was placed in the brachial vein. On arrival at the operating room, routine non-invasive monitors (blood pressure, ECG, peripheral SpO2, temperature) were placed in both babies. Before induction, N1 babies were given 0.03 mg of atropine intravenously. Our observation found no cross-circulation symptoms after atropine administration.

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Induction of anesthesia by incremental administration of sevoflurane was performed on N1. Four µg of fentanyl and 3 mg of propofol were given intravenously as an adjunct to facilitate intubation. We performed successful intubation using a 3.0 micro-cuffed endotracheal tube (ETT) in a lateral position. We performed the same procedure on N2. After intubation, intra-arterial blood pressure (IABP) was placed in the femoral arterial of both babies under ultrasound guidance. Anesthesia was maintained using sevoflurane 2.0-3.0 vol%, with FiO_2 40% in oxygen and air mixture with a total flow of 4 L/min using Jackson Reese.

Infiltration of 1% lidocaine with epinephrine 1:200,000 was administered to the incision site before surgery. The second surgical and anesthesia team was already in the second operating room when the separation was almost completed. The separation surgery lasted for 20 minutes then we transferred the N2 to operating room 2. The total surgical time for both babies was 2 hours with minimal intraoperative bleeding. We immediately performed awake extubation when the surgery was completed. Both babies were transferred to the PICU after ensuring that the hemodynamics were stable and there were no anesthesia residuals in the recovery room. Administration of intravenous paracetamol 50 mg every 6 hours as postoperative analgesia resulted in pain scores of 3 on the FLACC scale in both babies. We found neither baby with surgical wound infection, nerves disorders, limb weakness, or autonomic disorders during hospitalization. Both babies were discharged on day 11 with negative SARS-CoV-2 results.

DISCUSSION

The incidence of pygopagus conjoined twins is around 19% (4) and is more common in females (5). The separation surgery of conjoined twins poses challenges for both surgeons and anesthesiologists (6). The separation surgery should not be performed during the neonatal period to facilitate safety, except in urgency or emergencies (1). Surgery performed during the neonatal period can increase mortality by 50% (7). The separation surgery at infancy can increase the chances of success. However, prolonged procrastination increases the risk of both physiological and psychological problems and increases complications and costs (1).

Peri-anesthesia management in conjoined twin separation includes pre-operative preparation, intra-, and postoperative management. Pre-operative preparation comprises the preparation for the baby and anesthesia equipment and task division for the anesthesia team in the operating room. Preparation for the baby can be divided into several stages. At birth, the resuscitation phase is necessary to stabilize the baby's condition during transportation to the referral center. The next stage is stabilization and diagnostics. Stabilization steps are needed to optimize the baby's condition until the separation surgery is performed (1). Exposure to nosocomial infections during the stabilization stage should be avoided. In our case, to prevent the risk of exposure to nosocomial infections, including being infected with SARS-CoV-2, the conjoined twins were hospitalized in a particular room with a separate nurse who was not in charge of treating other babies. Visits were limited to the baby's parents while maintaining health protocols.

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Diagnostic stages are needed to determine the unification site, unified organ system, concomitant complications, and airway assessment (8). Imaging studies can accurately determine occurring organ division and vascular anomalies. This imaging is essential in determining the surgical plan and prognostic information (5). On pygopagus conjoined twins, an abdominal and pelvic CT scan is required to assess whether organ systems are union. In our case, the CT scan did not show internal-vertebral-spinal organ fusion and shared-circulation.

Preparation of anesthesia equipment such as anesthesia machine, breathing circuit, laryngoscopes, monitors, infusion pumps, syringe pumps, fluid warmer, and temperature control device should be available for each baby (2,9). The anesthesia team's position and machine placement are discussed with the surgical team. The placement of all equipment in the operating room must be designed according to the type of conjoined twins. In pygopagus conjoined twins, the anesthesia machine is placed on the same side of the head of the operating table (9). All anesthesia equipment for each baby is marked with two different colors, likewise with the drugs used.

The presence of cross-circulation and difficulty in managing the airway should be considered when performing anesthesia induction (9,10). In our case, although the CT scan revealed no fusion of the organ systems, we performed an atropine test to confirm that there was no cross-circulation (1). Difficult intubation was commonly found in the thoracopagus type due to the position of the babies facing each other (11). In the pygopagus type, difficult intubation can occur due to the lateral position of the baby. After ensuring there was no cross circulation, we alternately performed anesthesia induction and intubation on both babies. In anticipating airway management difficulties, we intubated the baby under deep sedation using sevoflurane inhalation and intravenous adjuvant while maintaining spontaneous breathing. Anesthesia induction in conjoined twins can be performed both by inhalation and intravenously. It can be done by considering the presence or absence of intravenous access before induction, predicting difficulty in airway management, and the anesthesiologist's preference (9). Muscle relaxants can be administered after the airways of both babies have been secured (2). Intraoperative hemodynamic stability and circulating volume should be maintained. Determining the amount of blood loss from each baby is quite tricky, especially in conjoined twins with cross circulation (1,10). Fluid replacement and blood loss can be based on visible blood loss through a suction tube, weighed gauze, assessment of peripheral perfusion and urine production, serial hematocrit, measurement of intra-arterial blood pressure, and central venous pressure (1,9,10). Hypothermia should be avoided because of prolonged surgical duration, operating room temperature, and heat loss through surgical wounds (7,9). We covered both babies' bodies using a heating mattress and intravenous fluid warmers to prevent hypothermia.

Massive blood loss and replacement, long-duration surgical procedures, and pre-operative anatomical changes can cause postoperative problems (2,9,10). Long-duration surgical procedures, unstable hemodynamic conditions, and continuous blood loss in conjoined twins of thoracopagus type will require postoperative mechanical ventilation (2). In our case, because the

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unification was only in the skin and subcutaneous tissue and underwent a simple surgical procedure, we performed extubation as soon as the surgery was complete. Postoperative care was carried out in the PICU while maintaining hemodynamic stability, fluid and electrolyte balance, and preventing infection.

Anesthetic management in a conjoined twin is different from that of normal infants. In our case, although the fusion is only of skin and subcutaneous tissue and will undergo a simple surgical procedure, this is our first case regarding the separation of conjoined twins. Direct assistance by an experienced pediatric anesthesiologist team will be required. Because direct assistance by an experienced pediatric anesthetist team was not possible, we conducted consultations and discussions to manage conjoined twins with the pediatric anesthesia team of Dr. Soetomo Hospital with telemedicine since receiving a referral for conjoined twins to postoperative care. We conducted this telemedicine consultation using the WhatsApp messaging facility and the Zoom video conferencing (Zoom Version 5.0.2; Zoom Video Communications Inc., San Jose, CA, USA). Likewise, during surgery, intra-anesthesia assistance was carried out by teleanesthesia using the facilities of the WhatsApp messenger application. Dr. Soetomo's pediatric anesthesia team has been experienced in managing conjoined twins since 1975. Until 2017, this team has handled 85 cases of conjoined twins (1).

During the COVID-19 pandemic, remote consultation using communication technology has increased (12). Using an online communication system is also beneficial for continuing the anesthesia trainer education program during the pandemic (13). Telemedicine has been known since the 1970s.

The WHO defines telemedicine as the provision of health care services through communication technology for disease diagnosis and treatment and for continuing education of health care providers where distance is a constraining factor (14).

Teleanesthesia, which is the use of telemedicine in anesthesia, has grown in the last few decades. This development is inseparable from the support of advances in communication technology. Teleanesthesia was first reported in 2004 (14) as a pre-operative evaluation consultation on ten patients in a remote facility, carried out by a nurse using a camera (15). In the same year, an anesthesiologist based in Virginia reported an intraoperative telemonitoring on patients undergoing laparoscopic cholecystectomy surgery in Ecuador (16). In 2009, Fiadjoe et al. (17) reported the successful use of teleanesthesia in 2 cases of liver transplant surgery. The Philadelphia-based anesthesia team mentors the team in India. Using teleanesthesia provides benefits such as reducing travel costs, facilitating specific consultations for diagnosis, therapy, and prognosis, facilitating postoperative monitoring, ICU care and rehabilitation, and educational and training purposes (18).

Other aspects to be considered during managing conjoined twins are communication and teamwork, ethical and legal aspects, and media coverage. The management of conjoined twins involves many multidisciplinary team members. Good communication and cooperation are the keys to successfully managing conjoined twins (1,8). To obtain good coordination and division of tasks during the separation surgery,

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we performed two simulated surgeries with a doll and performed in the operating room before the surgery day. Each team performed its respective duties and roles (1).

Conjoined twins have always attracted the attention of both the public and the medical community. Excessive media coverage can negatively affect the patient's parents and burden the medical team (1). In our case, starting from the referral process to postoperative care, we did not publish the management of conjoined twins in the mass media out of respect for the rights of the patient's family. We published to the media the successful management of conjoined twin separation when both babies were discharged from the hospital (19).

CONCLUSION

Conjoined twin separation surgery presents challenges for pediatric anesthesiologists. Although fusion is limited to the skin and subcutis, the possibility of cross-circulation and the prediction of difficult intubation requires careful attention and monitoring. Teleanesthesia as consultation and assistance means from an experienced anesthesiologist team provides significant benefits for the anesthesiologist without experience in conjoined twin separation surgery. Good communication and teamwork are essential to successful management in conjoined twin separation surgery. Ethical and legal aspects involving parents and families and the right communication media can potentially construct and increase team spirit.

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Case Report

EFFECTIVENESS AND SAFETY OF PROLONGED NEEDLE DECOMPRESSION PROCEDURES IN TENSION PNEUMOTHORAX PATIENTS WITH COVID-19

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ABSTRACT

Introduction: Coronavirus disease-19 (COVID-19) has become a pandemic that is still ongoing today. This is a new challenge for health workers in handling emergency cases. Several COVID-19 patients arrived at the hospital with severe respiratory problems. Meanwhile, other pathological conditions causing respiratory failure must also be considered, such as pneumothorax. **Objective:** This study aimed to examine the effective emergency procedures to treat COVID-19 cases with tension pneumothorax. **Case report:** A 45-year-old male patient arrived with a referral letter from a pulmonologist with a diagnosis of simple pneumothorax and pneumonia. The patient also presented a positive SARS COV-2 PCR test result. The patient complained about a worsening of shortness of breath. A symptom of dry cough for 14 days was also reported. Chest radiograph examination subsequently indicated right tension pneumothorax. In the emergency ward, needle decompression procedure connected to the vial containing sterile intravenous fluids was performed. Re-examination of the chest x-ray demonstrated right pulmonary re-expansion. The patient was monitored and after four days, needle decompression was removed and no chest tube was inserted because complete resolution of the lungs had occurred. **Discussion:** This case illustrates that tension pneumothorax causes worsening of the patient's condition with COVID-19 diagnosis. In another case of tension pneumothorax in a COVID-19 patient, needle decompression of the 2nd intercostal space and the mid-clavicular line was performed as initial treatment followed by chest tube insertion as definitive treatment. However, in this case, chest tube approach was not carried out because the patient had demonstrated clinical and radiological improvement and a worsening condition had not occurred. **Conclusion:** Prolonged needle decompression connected to a vial containing sterile intravenous fluids as deep as 2 cm from the water surface is an effective procedure in the management of tension pneumothorax even without the installation of a chest tube.

Keywords: COVID-19; Needle decompression; Simple pneumothorax; Tension Pneumothorax; Water sealed drainage.

ABSTRAK

Pendahuluan: *Coronavirus disease-19* (COVID-19) telah menjadi pandemi yang masih berlangsung hingga saat ini. Hal tersebut menjadi tantangan baru bagi para tenaga kesehatan dalam penanganan kasus kegawatdaruratan. Pasien COVID-19 seringkali datang ke rumah sakit dalam keadaan gangguan pernafasan berat. Sedangkan keadaan patologi lain yang menyebabkan gagal nafas juga harus dipikirkan, salah satunya ialah pneumothorax. **Tujuan:** kami melaporkan kasus pasien terkonfirmasi COVID-19 disertai tension pneumothorax, penanganan kegawatdaruratan dibutuhkan untuk mencegah perburukan. **Laporan kasus:** Seorang laki-laki 45 tahun datang membawa surat rujukan dari dokter spesialis paru dengan diagnosis simple pneumothorax dan pneumonia. Pasien juga membawa hasil pemeriksaan PCR SARS COV-2 positif. Pasien mengeluhkan sesak nafas yang semakin memberat. Sebelumnya, pasien mengeluh batuk kering sejak 14 hari yang lalu. Kemudian dilakukan pemeriksaan foto radiologi thorax dengan hasil tension pneumothorax kanan. Di instalasi gawat darurat, dilakukan needle dekompresi yang dihubungan dengan botol berisi cairan infus steril. Pemeriksaan foto thorax ulang menunjukkan re-ekspansi pulmonal kanan. Pasien dipantau dan pada hari ke-4 pasca pemasangan dilakukan pelepasan needle dekompresi dan tidak dilakukan pemasangan chest tube karena paru telah mengalami resolusi sempurna. **Pembahasan:** Kasus ini menunjukan tension pneumothorax yang menyebabkan

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perburukan kondisi pasien dengan diagnosis utama COVID-19. Pada kasus lain yang telah dilaporkan tension pneumothorax pada pasien COVID19, dilakukan needle decompressi pada Space intercostalis 2 dan garis mid-klavikula sebagai tatalaksana awal yang kemudian diikuti oleh pemasangan chest tube sebagai tatalaksana definitif. Namun pada kasus ini tidak dilakukan pemasangan chest tube karena pasien telah mengalami perbaikan secara klinis dan radiologis serta tidak diikuti perburukan. **Kesimpulan:** Prolonged needle dekompresi yang disambungkan dengan botol berisi cairan infus steril sedalam 2 cm dari permukaan air merupakan prosedur efektif dalam tatalaksana tension pneumothorax walaupun tanpa diikuti pemasangan chest tube.

Kata kunci: COVID-19; *Needle decompression; Simple pneumothorax; Tension Pneumothorax; Water sealed drainage.*

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INTRODUCTION

Coronavirus disease (COVID-19) has been declared a pandemic by the World Health Organization (WHO) and is still ongoing throughout the world today, including in Indonesia. The high number of cases is a challenge for doctors and paramedics in handling emergency cases, such as the use of standardized personal protective equipment when administering drugs to COVID-19 patients (1).

COVID-19 patients generally arrive at the emergency ward with respiratory problems which may lead to respiratory failure and death. Diagnosis and treatment of life-threatening emergency cases must be carried out immediately by medical personnel despite the limitations of physical examination procedures due to the use of standard personal protective equipment, such as auscultation, percussion, palpation in the diagnosis of tension pneumothorax.

The diagnosis of tension pneumothorax in an emergency is established through a medical history and physical examination. However, during a pandemic, such examination is often not feasible, therefore chest radiography is an important procedure that may confirm a clinical diagnosis (2). The radiological examination may be performed to confirm the diagnosis but should not delay the emergency care of a patient with a life-threatening tension pneumothorax. In hemodynamically stable pneumothorax patients, a chest X-ray is possible to be performed immediately. However, if the patient's hemodynamic condition is unstable and accompanied by an acute respiratory failure, bedside ultrasound examination is the preferred alternative as immediate confirmation of the diagnosis (3).

COVID-19 patients generally experience various respiratory problems, including respiratory failure. However, doctors and medical personnel need to consider other causes of respiratory failure besides SARS-CoV2 infection, such as tension pneumothorax, pleural effusion, and pulmonary embolism.

This study highlights a case of a patient with confirmed COVID-19 with a progressive pneumothorax which progressed to a tension pneumothorax with progressively worsening shortness of breath. In this case, urgent emergency treatment was required for thoracic decompression to prevent further damage and worsening which may lead to death.

CASE REPORT

A 45-year-old male patient consulted a pulmonologist specialist and was diagnosed with simple pneumothorax and pneumonia. The patient was recommended for SARS COV-2 independent PCR examination and was referred to dr. Soedono General Hospital. After three days, the patient was admitted to the emergency ward of dr. Soedono General Hospital with a referral letter from the

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pulmonologist. The results of an independent SARS COV-2 PCR examination with a positive result for COVID 19 and a chest X-ray 3 days earlier with radiological readings of a right pneumothorax with lung collapse towards the hilum with pneumonia were also presented (Figure 1).

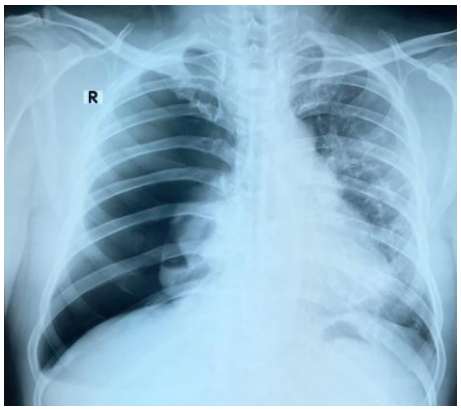

Figure 1. Right pneumothorax with lung collapse towards the hilum with pneumonia.

The patient reported a dry and frequent cough for more than 14 days and shortness of breath for 10 days. 3 days prior to admission to the emergency ward, the conditions worsened while patient was carrying out light activities such as walking few steps. The main complaint was a worsening of shortness of breath. The patient had not indicated symptoms of fever and had been an active smoker since young. The patient only had a history of dyspepsia and had no previous history of other serious illnesses. The patient had no history of chest trauma prior to the diagnosis of pneumothorax. The patient works as an office worker in a paint factory.

In the emergency ward, several medical personnel wore personal protective equipment and resuscitation equipment associated with initial emergency care. Physical examination indicated that the patient was compos mentis with normal general appearance. Clinically, the patient demonstrated shortness of breath with 36 breaths per minute, 94% oxygen saturation without oxygen supplementation, blood pressure of 112/91 mmHg, tachycardia of 119 beats per minute, and body temperature of 36.1^{o}C. Lung auscultation was not performed due to auscultation difficulty while in complete personal protective equipment. However, on percussion, hyper resonance in the right lung, decreased vocal fremitus, and minimal deviation of the trachea to the contralateral direction were detected.

Investigations

Anteroposterior chest radiological examination was performed and the results demonstrated a wide right tension pneumothorax with tracheal deviation and mediastinal shift to the contralateral direction and the left lung was compressed as illustrated in Figure 2.

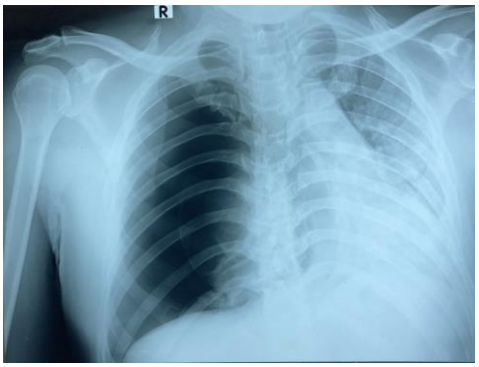

Figure 2. Right Tension Pneumothorax, tracheal deviation, and pneumonia.

The patient's complete blood on arrival at the ER indicated hemoglobin level of 14.5 g/dL, Platelets of 325x103/µL, Hematocrit of 44.1%, Leukocyte Count of 8.10x103/µL with Eosinophils at 4.9% (normal range 0-3%), Basophils at 1.2% (normal range 0-1%), Neutrophils at 57.6% (normal range 50-62%), Lymphocytes at 27.8% (normal range 25-40%) and monocytes at 8.4% (normal range 3 -7%). Neutrophil Lymphocyte Ratio (NLR) was at

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2.1 and Absolute Lymphocyte Count (ALC) at 2252.

Table 1. Laboratory Findings and Blood Gas Analysis.

Laboratory parameters	On arrival	Shortly after thoracocentesis	Next day
Hb	14.5	-	14.3
Platelets	$325x10^3$	-	$316x10^3$
Hematocryte	44.1%	42%	41%
Leukocyte	$8.10x10^3$	-	$7.72x10^3$
Eosinophils	4.9%	-	4.8%
Basophils	1.2%	-	0.5%
Neutrophils	57.6%	-	61.7%
Lymphocytes	27.8%	-	25.1%
Monocytes	8.4%	-	7.9%
Neutrophil Lymphocyte Ratio (NLR)	2.1	-	2.5
Absolute Lymphocyte Count (ALC)	2252	-	1938
D-dimer	-	-	2771.48
pH	-	7.4	7.36
pCO2	-	45	53
pO2	-	109	179
Na+	-	133	134
K+	-	3.8	3.9
Ca++	-	1.14	1.15
Glucose	-	103	87
Lactate	-	0.7	0.6
SO2	-	98%	100%

Blood gas analysis with arterial blood samples shortly after needle thoracocentesis indicated pH of 7.40, pCO2 of 45 mmHg, pO2 of 109 mmHg, Na+ of 133 mmol/L, K+ of 3.8 mmol/L, Ca++ of 1.14 mmol/L, Glucose of 103 mg/dL, Lactate of 0.7 mmol/L, Hematocrit of 42%, and SO2 of 98%.

The following day, patient's complete blood count was monitored. The results indicated Hemoglobin of 14.3 g/dL, Platelets of 316x103/uL, Leukocyte Count of 7.72x103/uL, Eosinophils of 4.8%, Basophils of 0.5%, Neutrophils of 61.7%, Lymphocytes of 25.1%, Monocytes of 7 ,9%, D-dimer of 2771.48 ng/mL, NLR of 2.5 and ALC of 1938. Blood gas analysis was performed with arterial blood samples and the results indicated pH of 7.36, pCO2 of 53 mmHg, pO2 of 179 mmHg, Na+ of 134 mmol/L, K+ of 3.9 mmol/L, Ca++ of 1.15 mmol/L, Glucose of 87 mg/dL, Lactate of 0.6 mmol/L, Hematocrit of 41%, and SO2 of 100%.

Differential Diagnosis

Differential diagnosis of respiratory disorders with a history of upper respiratory tract infection in the pandemic era should be considered as COVID-19 until proven otherwise. Tension pneumothorax may occur due to COVID-19 (3). An important differential diagnosis with similar symptoms is pulmonary embolism. Patients with pulmonary embolism generally experience hypoxia, tachycardia, and often worsen if not treated immediately. Pulmonary embolism may also be a complication of COVID-19 causing acute deterioration in patients (4). COVID-19 may cause pulmonary embolism through several possible mechanisms, namely a severe inflammatory response and DIC may occur in COVID-19 patients, resulting in micro and macrovascular pulmonary thrombosis. A local virus-induced inflammatory reaction may also cause damage to the vessel wall (5).

Treatment

Based on clinical physical examination and medical history accompanied by diagnosis confirmation in the form of a chest X-ray, needle decompression was immediately performed for right tension pneumothorax using a size 16 cannula inserted in the 2nd intercostal space and mid-clavicular line. The 16-gauge cannula was subsequently connected using a macro set infusion tube which was connected to a bottle containing sterile infusion fluid at a position 50 cm below the patient and the end of the tube was 2 cm deep from the surface of the water in the bottle. The outgoing air exited in the form of air bubbles in sterile infusion fluid

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during the decompression process. In performing the needle decompression procedure, insertion of a chest tube was prepared as the next treatment. However, it was not carried out since the patient experience clinical and radiological improvement. Rigorous evaluation was carried out periodically instead.

Results and Follow-Up

Emergency management of needle thoracocentesis resulted in immediate improvement in the patient which was characterized by re-expansion of the right lung from radiological examination (Figure 3), clinical improvement in the form of increased oxygen saturation to 99-100%, as well as respiratory physiology improvement in the form of decreased respiratory rate and normalization of heart rate. The patient was subsequently admitted to the COVID-19 ward due to a positive PCR result.

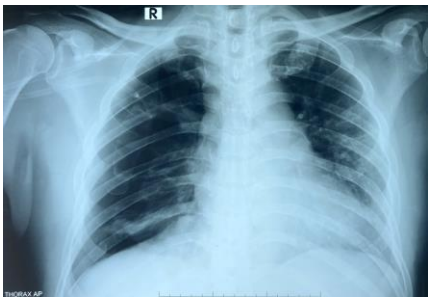

Figure 3. Right pneumothorax improved and pneumonia was minimal

After needle thoracocentesis procedure, the patient was still provided with oxygen supplementation in the form of NRM 10 lpm to support optimal oxygenation. The following day after the admission to the ward, patient's conditions did not deteriorate clinically or radiologically (Fig. 4). Hence, the oxygenation was reduced using a nasal cannula from 2-5 Lpm. On the 3rd day of treatment, the patient did not use any oxygen supplementation since the capillary oxygen saturation had stabilized and no symptoms related to the respiratory system were detected. On the 4th day of treatment, the needle thoracocentesis in the right intercostal midclavicular line which had been connected to a bottle filled with sterile intravenous fluids was no longer inflated and, radiologically, there was no deterioration (Fig. 5). Therefore, a removal was performed and a chest tube was not installed since the patient had already been in a good condition and the lungs had undergone complete resolution without any respiratory-related symptoms requiring further invasive treatment in the form of a chest tube.

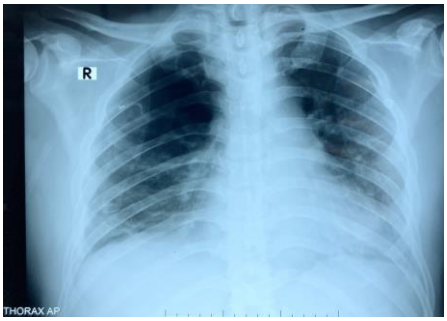

Figure 4. Right pneumothorax improved and pneumonia was minimal

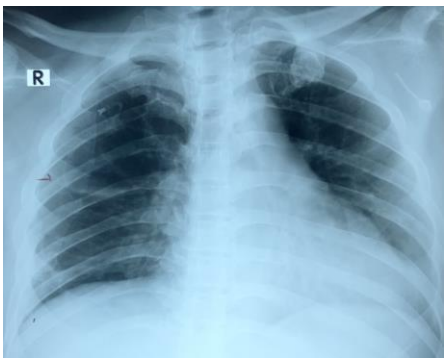

Figure 5. Minimal right pneumothorax

This procedure is not a standard treatment for pneumothorax, but it may be performed considering its effectiveness and the complications of the case. Effectiveness may be determined by clinical improvement, radiological improvement. and regular close

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laboratory monitoring. If this approach does not provide immediate clinical, radiological, or laboratory improvement, a chest tube installation must be carried out.

On the 9th day of treatment, a chest X-ray was performed to evaluate the lung condition related to post-needle thorachocentesis in tension pneumothorax. This is necessary to establish an early diagnosis of recurrent pneumothorax. The results of the final chest radiological examination did not indicate a pneumothorax and lung expansion seemed optimal (Figure 6). Based on several considerations, such as clinical parameters, the patient was asymptomatic, whereas laboratory examinations and the SARS COV-2 PCR examination indicated negative results. On the 10th day, the patient was released for outpatient treatment.

In this case, a follow-up of 14 days after discharge was carried out and there were no complaints and symptoms associated with recurrent pneumothorax or other respiratory syndroms. It was reported that the patient was able to continue his usual physical activities.

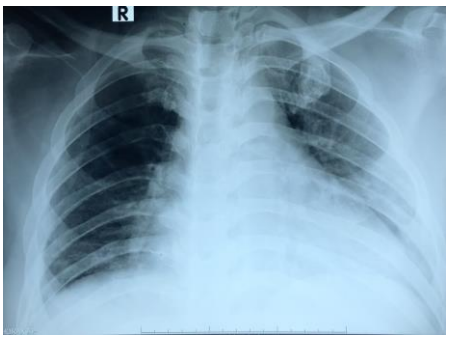

Figure 6. Chest X-ray showed no abnormalities and pneumothorax

DISCUSSION

This case highlights a tension pneumothorax that causes the patient's condition to worsen with COVID-19 primary diagnosis. Diagnosis of pulmonary pathology due to COVID-19 is very important to direct the appropriate therapy. If correct diagnosis is delivered, it may result in inappropriate treatment and life-threatening consequences. This study could not confirm whether the pneumothorax in this patient was due to COVID-19 infection or whether the two diseases simply coexisted (4).

Pneumothorax is divided into two types, namely primary and secondary. Primary pneumothorax is a pneumothorax that occurs without a clear cause and no other underlying disease. Several risk factors that may increase the occurrence of primary pneumothorax include smoking habits, gender, and family history of pneumothorax. Secondary pneumothorax, on the other hand, occurs due to other lung pathologies. Secondary spontaneous pneumothorax may occur in the presence of COPD, pulmonary tuberculosis, necrotizing pneumonia, and ARDS (6,7).

The prevalence of pneumothorax in COVID-19 patients is 1-2%. ARDS in COVID-19 may lead to complications of spontaneous pneumothorax due to volume- and pressure-related alveolar rupture (8). Histological examination of lung biopsy samples taken from patients who died from COVID-19 revealed desquamation of pneumocytes and formation of hyaline membranes suggestive of ARDS (7). Therefore, structural changes due to SARS-CoV-2 infection may cause secondary spontaneous pneumothorax complications.

The most common symptoms of a pneumothorax are shortness of breath and chest pain that may radiate to the chest or ipsilateral shoulder. Physical examinations generally detect increased respiratory rate, asymmetric chest expansion, decreased tactile fremitus, hyper resonant percussion, and decreased lung breath sounds. Investigations that may be carried out include a chest X-ray. Chest X-ray may detect that the ipsilateral lung has collapsed and that the mediastinum shifts to the contralateral side (9). If patient is

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in unstable condition, diagnosis confirmation may be made by ultrasonography (USG), if available (10). If patient is in a stable condition and the diagnosis could not be determined from a chest X-ray, a chest CT scan may be performed. However, this examination is not recommended to be carried out routinely (2).

In another reported case of tension pneumothorax in a COVID-19 patient, needle decompression of the 2nd intercostal space and the mid-clavicular line was performed as initial treatment followed by chest tube insertion as definitive treatment (2). Presently, chest tube is the definitive therapy in pneumothorax cases (6). However, in this case, no chest tube was attached and only a decompression needle was connected to a bottle containing sterile IV fluids as deep as 2 cm from the surface of the water (water seal drainage). This step was selected because the patient had experience clinical and radiological improvement and a worsening did not occur afterwards.

A water shield drainage system was carried out by connecting a needle catheter that has been inserted into the pleural cavity with an infusion set (i.v. line) which on the other end was immersed in a sterile fluid (infusion fluid or 500-1000ml aqua dest) as deep as 2 cm. Sterile fluid was placed $\pm$60 cm below the puncture hole. The end of the IV line that was immersed into the sterile fluid aimed to keep the pleural cavity at a pressure of $\pm$2 cm H2O. When the air pressure in the pleural cavity exceeded 2cm H2O (tension pneumothorax), the pressure would subsequently be released as bubbles through the system. The distance of 60cm between the puncture hole and sterile fluid aimed to prevent fluid from entering the pleural cavity during the inspiration phase.

During the pandemic, when treating patients with respiratory failure, there have been tendencies to assume the diagnosis as COVID-19. However, other possible diagnoses that may cause respiratory failure conditions must still be considered. In addition, routine auscultation is difficult to carry out due to concerns regarding the transmission of SARS-CoV-2 infection and the use of personal protective equipment that may limit the examination (4). This condition did not cause delays in providing emergency care to patients with life-threatening tension pneumothorax.

CONCLUSION

In this case, prolonged needle decompression connected to a bottle of sterile intravenous fluids 2 cm from the water surface (water seal drainage) is an effective procedure in the treatment of tension pneumothorax not followed by chest tube insertion.

Evaluation of the effectiveness of this method was carried out through close observation of clinical conditions, radiological and laboratory evaluations regularly. In this case, four days of installation demonstrated improvements. This procedure illustrates good efficacy, although preparation of chest tube insertion equipment as definitive therapy must be available and easily accessible.

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Literature Review

THREE-WAY STOPCOCK AS BREATHING CIRCUIT IN ANESTHETIC PROCEDURES ON WISTAR RATS AS ANIMAL MODELS IN RESEARCH

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ABSTRACT

Introduction: General anesthesia in experimental animals is not limited in the field of anesthesia research. In Indonesia, ventilators and breathing circuit systems utilized in research involving anesthesia in rats are not widely available. The limitations in using ventilators and breathing circuit systems in research are one of the reasons why Indonesia is lacking complex and advanced animal experimental studies. **Objective:** This study aimed to examine a general anesthesia procedure for intubation in rats using tools and materials commonly discovered in clinical settings. **Method:** A search on the PubMed database using keywords consisting of animal study, rats, anesthesia, breathing circuit was performed. **Review and Discussion:** An endotracheal tube insertion procedure may utilize a Miller size 0 laryngoscope, while the endotracheal tube may use a 16 G intravenous cannula in which the needle is replaced by a small wire. The 3-way stopcock system may be considered as a replacement for the Mapleson E system for the breathing circuit system. The Fresh Gas Flow (FGF) source needs to be connected to the angled port, while the other two ports are connected to the reservoir and the intravenous cannula which would be delivered to the experimental animals. FGF three to five times as much as the minute ventilation may be used and the use of a reservoir capacity is similar to the tidal volume of spontaneous ventilation. Therefore, the oxygen flow rate is set to approximately 1-1.5 L per minute. A reservoir is not required for controlled ventilation. **Conclusion:** The use of a 3-way stopcock as a non-rebreathing circuit system is effective because it utilizes the similar principle as Mapleson E. The ability to use common tools and materials for general anesthesia procedures would significantly boost research of animal models in Indonesia to a further level.

Keywords: Anesthesia; Animal Model Research; Breathing Circuit; Medicine; Rats; Research Laboratory

ABSTRAK

Pendahuluan: Prosedur anestesi umum yang digunakan pada hewan coba tidak terbatas pada penelitian di bidang anestesi. Ventilator dan sistem sirkuit pernapasan untuk penelitian yang melibatkan prosedur anestesi pada tikus terbatas di Indonesia. Keterbatasannya menjadi salah satu alasan kurangnya studi eksperimental hewan yang kompleks dan canggih di Indonesia. **Tujuan:** Penulis ingin membahas prosedur anestesi umum intubasi pada tikus menggunakan alat dan bahan yang sudah tersedia dalam praktik klinis sehari-hari. **Metode:** Kami melakukan pencarian di pangkalan data PubMed menggunakan kata kunci yang terdiri dari studi hewan, tikus, anestesi, sirkuit pernapasan. **Review dan Pembahasan:** Prosedur pemasangan selang endotrakeal dapat menggunakan laringoskop Miller ukuran 0. Selang endotrakeal menggunakan kanula intravena 16 G di mana jarum diganti dengan kawat kecil. Sistem *3-way stop cock* dapat digunakan sebagai pengganti sistem Mapleson E untuk sistem sirkuit pernapasan. Sumber aliran gas anyar (AGA) akan terhubung ke porta bersudut, sementara dua porta lainnya akan terhubung ke reservoar dan kanula intravena ke hewan eksperimental. Kami menggunakan AGA 3-5 kali lebih banyak dari ventilasi menit dan penggunaan kapasitas reservoar yang mirip dengan volume tidal untuk ventilasi spontan. Oleh karena itu, laju aliran oksigen diatur menjadi sekitar 1-1,5 L/menit. Reservoar tidak diperlukan untuk ventilasi terkontrol. **Kesimpulan:** Penggunaan *3-way stop cock* sebagai sistem sirkuit *non-rebreathing* menggunakan prinsip Mapleson E. Memanfaatkan ketersediaan alat dan bahan dalam praktik sehari-hari untuk prosedur anestesi umum akan membawa penelitian model hewan di Indonesia ke tingkat yang lebih lanjut.

Kata kunci: Anestesi; Penelitian Model Hewan; Sirkuit Pernapasan; Kedokteran; Tikus; Laboratorium Penelitian

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INTRODUCTION

General anesthesia procedures used in animals are not limited to research in the field of anesthesia. Research requiring post-procedure recovery of the animal models needs general anesthesia that maintains the physiological state of the models. The role of a ventilator equipped with a precise breathing circuit is therefore significant in maintaining the physiological respiratory system of the animal models during the procedure.

Ventilators and breathing circuit systems for research involving anesthesia procedures in rats are not widely available in Indonesia. Indonesian Medical Education and Research Institute (IMERI) is possibly the only institution in Indonesian with an anesthetic delivery system facility manufactured by Harvard (http://imeri.fk.ui.ac.id/equipment/). However, the use is merely limited to delivering anesthetic gas through the gas chamber. The limitations of ventilator and breathing circuit system are one of the reasons why Indonesia is lacking in complex and advanced animal experimental studies. In addition, these studies require the use of intubation procedures and the administration of artificial ventilation.

Therefore, this study aimed to examine general anesthesia procedures in rats using tools and materials that are easily available in the clinical settings. It is hoped that, through this study, future research in the field of anesthesia in Indonesia may further advance in using animal models.

METHOD

A search in PubMed database using keywords consisting of animal study, rats, anesthesia, breathing circuit was performed. References of various studies were also evaluated to identify additional relevant examination.

LITERATURE REVIEW

Wistar rats (Rattus norvegicus) are frequently used as animal models since the required treatment is relatively simple and economical. Being an animal model of cardiovascular pathology research contributes to understanding and providing treatment to a broad range of medical conditions. Specifically, in the context of acute myocardial infarction (AMI), rat models have been commonly used in studies of pathogenesis, investigations, and novel therapies, although there were often difficulties in translating experimental findings to clinical benefits. However, in recent years there have been two important changes in clinical approaches to AMI. First, there has been an increasing recognition of the pathophysiology in human AMI which has occurred at numerous levels, not merely within the epicardial coronary artery, but also within the microvasculature and the myocardium. Second, contemporary treatments are shifting from the thrombolytic dissolution of epicardial coronary thrombus to direct mechanical approaches using angioplasty and stents. These changes in the understanding of AMI present implications for the relevance of these animal models. The following discussions will review and examine the current rat models of AMI, place them in a clinical context, observe their advantages and limitations, as well as outline possible future developments, providing an

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overview of the place of these important models of AMI (1). Male adult rats approximately weigh 300-500 grams, while female adults approximately weigh 250-300 grams. Their respiratory rate ranges from 7 to 160 times per minute, depending on their agility. A minute ventilation of the strain is reported to be approximately 303 ml/min or 83 ml/100 gr/min (2). The tidal volume varies between 2.5 ml and 4.5 ml. Inspiration expiration ratio is reportedly close to 1:1.3 (3). Several studies created ventilator settings with a tidal volume of 6 ml, respiratory rate of 60 times per minute, and inspiration:expiration ratio of 1:1 (4). Previous study utilized tidal volume settings of 3-5 ml and respiratory rate of 72 times per minute (5).

Research may utilize Wistar rats as animal models in the anesthesia field. For example, a study used a tibial nerve injury model of mice to examine the effect of dorsalis radix modulation on chronic pain (6). The procedure of creating tibial nerve injuries and implantation of stimulation electrodes in the dorsalis ganglion required a general anesthesia procedure using inhaled gas delivered through the nose cone or gas chamber. Another advanced example is a study towards the efficacy of various ventilation strategies to prevent lung damage in abdominal surgical animal models (7). This study required general anesthesia procedures using intubation and muscle relaxant agents during abdominal surgical procedures.

General anesthesia induction may be carried out by administering either intravenous or inhalation of anesthesia agents. Intravenous anesthesia agents are relatively simple to administer, but difficult to administer continuously if the injection area is covered in sterile cover during a surgical procedure (8). This may be overcome by the administration of volatile gas of anesthesia which also offers a faster recovery period. However, breathing maintenance remains a priority during the procedure, especially for complex procedures, such as model creation through cardiac or brain surgery.

The absence of advanced anesthesia devices in Indonesia has served as an obstacle in the advancement of animal model study using general anesthesia procedures. General anesthesia is commonly administered through the anesthetic gas delivery system through a non-rebreathing breathing circuit connected to the rat's airway using a nosecone. However, the nosecone is not able to maintain the patency of the airway during the procedure.

The intubation procedure is an alternative that requires the rats to be extubated and regain consciousness, which differs from tracheotomy. Intravenous cannula without needles may be used as endotracheal tubes. The narrowest passage of the larynx is reportedly located at the glottis with a diameter of approximately 1.5 mm (9). Therefore, an intravenous cannula with the size of 16G and an internal diameter of 1.4 mm may be selected. Needles on intravenous cannula are replaced with small wires to avoid the risk of trauma. The larynx is located approximately 1.75 cm from the hard palate arch by forming a 35-degree angle on the sagittal field connecting the hard palate arch and mandibles as high as inferior incisor teeth when the mouth is wide open. Therefore, a small wire, serving as a stylet, is bent by 145 degrees at a point of 1.75 cm from the end to facilitate the insertion into the larynx. Carina is located about 35 mm from the glottis or approximately 52 mm from the hard palate arch, hence insertion using an intravenous cannula of 16 G with a length of 45 mm

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would provide sufficient depth without the risk of exceeding the carina position.

The insertion of an endotracheal tube may utilize Miller's laryngoscope size 0 (see figure 1) (10). This laryngoscopy was selected since anesthesiologists had become accustomed to the tool. The aid of an assistant is necessary to hold the upper incisor teeth with a thread and pull the tongue towards the ventral using the other hand. Glottis is usually covered by a soft palate when the tongue has been pressed by the laryngoscopy blade towards the ventral. When inserting an intravenous cannula, the glottis will be exposed when the cannula is inserted by slightly pressing the hard palate.

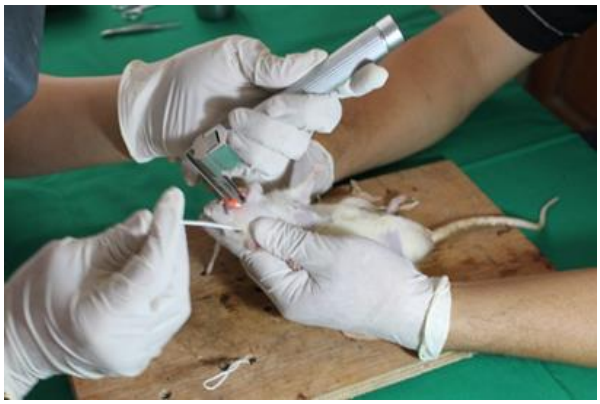

Figure 1. Intubation using Miller laryngoscope size 0

Following intubation, an intravenous cannula need to be connected to the breathing circuit system. The main problem is the availability of anesthesia delivery systems or breathing circuits that are easily available in daily practice. A three-way stopcock system may be used as a replacement for the Mapleson E system. The three-way stopcock would function as a t-piece. The fresh gas flow (FGF) source is subsequently connected in the angled port, while the other two ports are connected to the reservoir and intravenous cannula to the animal model (see figure 2). This aims to maintain positive pressure during expiration through the administration of FGF and avoid the formation of venturi effects which would cause atmospheric gases to be inhaled. The 3-way stopcock shape with a 90-degree angle carries an advantage. If the FGF port is angled towards the endotracheal tube, continuous positive pressure would form and increase resistance. If the angle leads to the reservoir, a venturi effect may form causing sub-atmospheric pressure.

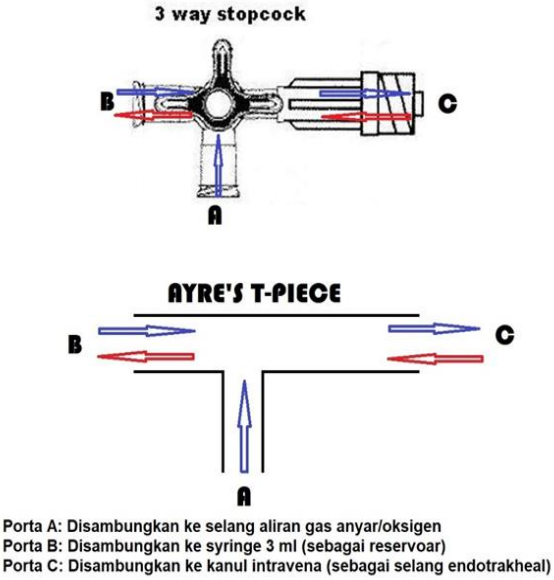

Figure 2. The adoption of Ayre's t-piece principle on 3-way stop cock

To understand the breathing system using Mapleson E, the respiration phase needs to be divided into 3 parts, namely: the inspiration phase, the expiration phase, and the final pause of the expiration (11). When the inspiration for spontaneous ventilation, the FGF would be entirely inhaled if the FGF exceeds the peak inspiratory flow rate (PIFR). If the FGF rate is less than PIFR, the inhaled gas is a mixture of FGF-derived gas and gas found in the expiratory arm. During the expiration phase, FGF and exhalation gas would flow into the reservoir arm to be disposed into the atmosphere. At the end of

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the expiratory phase, the FGF would rinse the remaining gas and fill the reservoir arm.

The use of a 3-way stopcock would result in an additional dead space of fewer than 0.1 ml. This additional dead space is located from the end of the port connected to the intravenous cannula to the stopcock. This is calculated at a minimum. If a nosecone is used, the dead space would increase significantly, hence the volume of inhaled air increases as well.

Reservoir uses a 3 ml syringe without a plunger. According to the principle of Mapleson E, the use of a reservoir with a minimum volume of tidal volume would minimize the inhalation of atmospheric gases when inspiring at spontaneous ventilation. The 3 ml syringe was selected since the diameter is not large enough to prevent the mix of atmospheric gases and exhalation gases in the reservoir.

In the use of Mapleson E, the FGF rate need to exceed PIFR to ensure that no dilution of anesthetic gas due to inhalation of atmospheric gases occurs and prevents the rebreathing of gases in the expiratory arm. A study reported that mice had PIFR of up to 100 ml/s or 6 L/min (3). The reservoir decreased the need for FGF rate to prevent inhalation of atmospheric gases during spontaneous ventilation inspiration. However, the FGF rate need to equally ensure rinsing mixed air in the reservoir during the expiation phase. An oxygen flow speed of 6 L/min would be equivalent to PIFR, ensuring no anesthesia gas dilution and rebreathing. However, gas wastage may become an issue.

Optimal FGF rate determination on spontaneous ventilation depends on respiratory rate, minute ventilation and expiratory arm capacity (12). Since the pause of end-expiration must have been very short on the spontaneous ventilation of rats, the FGF rate required more than minute ventilation to ensure the rinsing of the exhalation gas before the start of the inspiration phase. The FGF rate should be at least a minimum rate of 2.5-4 times when using a tidal volume-sized expiratory arm (13). FGF rate of 3-5 times a minute ventilation and reservoir as much tidal volume for spontaneous ventilation may be used. Therefore, the oxygen flow rate is set to be approximately 1-1.5 L/min.

The anaesthesia gas delivery system may use a simple anesthesia machine consisting of oxygen sources, pressure regulators, flowmeter, evaporator containing volatile anesthetic gases, port to the nonrebreathing system (14). Controlled ventilation may be performed by closing the reservoir tip using the finger with a ratio of the duration of the inspiration phase and expiration in rats generally at 1:1. The reservoir is not required on controlled ventilation because atmospheric gas inspiration and re-inhalation do not occur, as has been carried out by Nugroho et al (15).

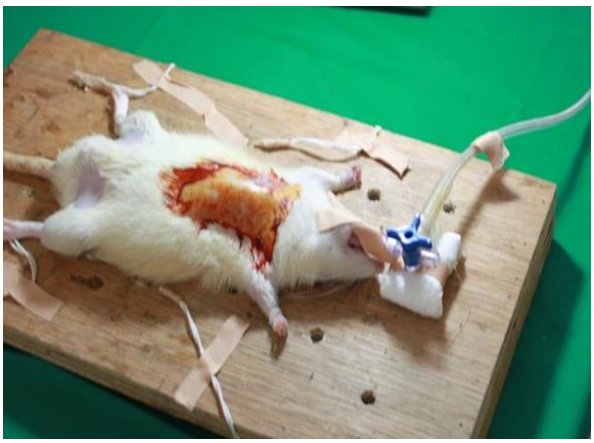

Figure 3. The application of 3-way stop cock on controlled-ventilation general anesthesia procedure

The breathing system using a 3-way stopcock presents several drawbacks. The

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controlled ventilation would become more difficult by manual ventilation to ensure the long accuracy of the inspiration and expiration phases. The closure of the reservoir tips every half second is certainly difficult to achieve constantly. Intrapulmonary pressure could not be well controlled, hance may injure the lungs of animal models. Estimation of flow rate settings was extrapolated from studies of flow rates in humans. This certainly does not take into account the duration of each respiration phase. The risk of rebreathing and waste of gas needs to be further studied using gas analysis for this method to be developed into a standard procedure. The study of resistance formed during the expiration phase is also required.

CONCLUSION

The use of a 3-way stopcock as a non-rebreathing circuit system is effective since it employs similar principle as Mapleson E. The ability to use common tools and materials for general anesthesia procedures would bring research of animal models in Indonesia to a further level.

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