the correlation between surfactant protein-D

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THE CORRELATION BETWEEN SURFACTANT PROTEIN-D (SP-D) SERUM LEVEL AND INTUBATION TIME ON COVID-19 PATIENTS IN INDONESIA

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ABSTRACT

COVID-19 patients with ARDS who are admitted to the ICU needed tracheal intubation and mechanical ventilation, where the tracheal intubation strategy as early as possible with the good protocol ventilation management produce favorable patient outcomes. In performing the intubation needed to consider the right time to produce optimum outcome. The increase of Surfactant Protein-D serum level is a specific indicator of lung injury with severe ARDS and the duration of intubation. From that, the aims of this study to determine the correlation between Surfactant Protein-D (SP-D) and intubation time on COVID-19 patients. This observational analytic research with retrospective cohort design is conducted during March-August period and has obtained the ethics certificate from the Ethical Committee of Dr. Soetomo Surabaya. The examination of Surfactant Protein-D level is conducted on patients who have met the inclusion and exclusion criteria and the intubation time is recorded. In this research obtained 28 patients, where 20 patients are male and 8 patients are female. The comorbid factor that most affect the patient's condition is Diabetes Mellitus. The average of Surfactant Protein-D serum level is 42,15 ng/ml (SD ± 32,71 ng/ml). The statistics analysis results showed that there is no meaningful correlation between Surfactant Protein-D serum level and intubation time (p: 0,304). In addition, it is also found that the SP-D level results which has no meaningful difference in the group of patients who died and survived (p: 0,159). The examination of Surfactant Protein-D level did not show a meaningful correlation with intubation time on Covid-19 patients.

1. INTRODUCTION

On December 31, 2019 in Wuhan, China, symptoms of pneumonia with 25% unknown causes were reported to the World Health Organization (WHO). This pneumonia is caused by severe acute respiratory

syndrome coronavirus-2 (SARSCoV-2) which causes coronavirus disease (COVID-19). As of July 20, 2020, it is known that there have been more than 14 million cases of COVID-19 and nearly 600,000 deaths reported worldwide [1]. The COVID-19 pandemic is not over, it has even surpassed SARS in 2003 and MERS in 2012 [14]. As of December 2020, the number of people diagnosed with COVID-19 worldwide surpassed 76 million; while the case fatality rate in 219 countries and territories was 2.3%. In comparison, SARS infected 8,096 people in 29 countries from November 2002 to July 2003 and had a case fatality rate of 9.6%, while MERS infected 2,494 people in 27 countries from April 2012 to November 2019 and had a case fatality rate of 34.4% [15]. The first case of COVID-19 in Indonesia was reported on March 2, 2020 and as of December 12, 2020 there have been 617,820 confirmed cases (CFR 3.0%). In East Java, Indonesia, 69,130 positive cases have been recorded and 4,879 deaths have been reported. The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) has reported that nearly one fifth of hospitalized Covid-19 patients require level 2 and 3 care and between 58% and 88% of patients admitted to the ICU require tracheal intubation and mechanical ventilation. In total, 165 patients included in the study confirmed positive for COVID-19, 127 of whom were patients who received primary tracheal intubation, with the remainder either unknown or negative. Reported a prospective observational cohort study of 200 patients with COVID-19 who required tracheal intubation had 30-day survival (as many as 70% of cases). The study emphasized that elevated SP-D levels were considered a specific indicator of lung injury in both adults and premature infants, and were significantly associated with severe PARDS, respiratory failure, and duration of intubation. Patients with ARDS had higher plasma SP-D levels (median 20.8 ng/mL; $p < 0.01$) and higher in-hospital mortality ($p < 0.001$) than those without ARDS. The cut off value of 12.7 ng/mL for SP-D resulted in a sensitivity of 74% and a specificity of 63%. High SP-D levels within 48 hours of ICU admission may serve as a diagnostic marker for ARDS.

The decision to intubate a COVID-19 patient requires careful consideration by the doctor who treats the patient. The Chinese Society of Anesthesiology Task Force on Airway Management published recommendations for the management of intubation in COVID-19 patients. Based on Pontoppidan's recommendation, it was explained that patients will be intubated if they experience a respiratory rate above 35 breaths per minute, poor oxygenation parameters (PaO2 and FiO2 ratios less than 200), ventilation criteria PaCO2 more than 60. These criteria are still considered empirical criteria because they are not yet available. further studies or research regarding the criteria for intubation in COVID-19 patients. From the study conducted by there is a close relationship between the accumulation of oxygen debt for 48 hours and the survival rate of patients in the ICU. This shows that intubation time is an important variable in overcoming oxygen depth. In performing intubation, it is also necessary to consider the risk of "ventilator inflicted lung injury" (VILI) where this mechanism damages the epithelium, endothelium, extracellular matrix and airway pathways so as to increase mortality. To prevent VILI, as an anesthesiologist, you should not intubate too early to prevent this from happening. On the other hand, when the patient is not intubated, the patient will be at risk of experiencing respiratory distress, excessive inspiration to compensate for impaired oxygenation and ventilation so that self-inflicted lung injury can occur, as an anesthesiologist this becomes a dilemma, when is the right intubation time that produces the optimum outcome between the two. these and other risks. From that, the aims of this study to determine the correlation between Surfactant Protein-D (SP-D) and intubation time on COVID-19 patients.

2. METHOD

This study is an observational analytic study with a retrospective cohort design that aims to determine the relationship between serum surfactant-D (SP-D) levels and the time of intubation of COVID-19 patients in the RES and RIK rooms at Dr. Soetomo Surabaya, Indonesia. The research location chosen by the researcher was in the Resuscitation Room and Special Infection Room at Dr. Hospital. Soetomo Surabaya,

Indonesia, where the research was conducted after obtaining approval from the ethics committee of RSUD Dr. Soetomo Surabaya. The target population for this study was confirmed adult Covid-19 patients who were intubated. Meanwhile, the affordable population in this study were confirmed adult Covid-19 patients who were intubated in the Isolation Room of RES and RIK RSUD Dr.Soetomo Surabaya, Indonesia. The criteria for this study are divided into two, namely inclusion and exclusion criteria. Inclusion criteria, namely, first, confirmed COVID-19 patients who underwent intubation procedures and underwent treatment in the RES Room and Special Infection Room at Dr.Soetomo Surabaya, Indonesia. Second, confirmed COVID-19 patients aged 18 to 65 years. Third, they have received information about the research and the purpose of this research (listed in the information for consent) and are willing to participate (signed the informed consent). Meanwhile, the exclusion criteria are, first, patients who have never been intubated during treatment. Second, patients with a history of COPD or asthma. Third, patients who were reintubated. Fourth, patients with ROX index < 2.85 at the time of admission to RIK.

3. RESULTS

A retrospective search of data in RES and RIK 1 from March to August 2020 found a total of 28 Covid-19 patients who received intubation and mechanical ventilation. All patients in this study had their serum levels of Surfactant Protein-D (SP-D) checked. There were no research subjects who experienced drop-out, it can be checked in table 1.

Table 1. Subject Criteria.

Age (year)		51,17±11,9
21-30	2 (7,14)	
31-40	1 (3,58)	
41-50	10 (35,7)	
51-60	10 (35,7)	
61-70	4 (14,3)	
> 71	1 (3,58)	
Sex		
Men	20 (71,4)	
Women	8 (28,6)	
PF ratio		109,34±40,66
<100	14 (50)	
100-200	14 (50)	
SOFA Score		5,57±2,28
<9	26 (92,8)	
9-11	1 (3,6)	
>11	1 (3,6)	
Mortality	23 (82,1)	
Survive	5 (17,9)	

3.1 Serum Surfactant Protein-D (SP-D) Levels and Intubation Time

Through the results of a study on 28 patients, the results of Surfactant Protein-D levels and when to intubate Covid-19 patients were obtained after admission to the treatment room. Characteristics of serum SP-D levels are known with a minimum value of 8.03 ng/mL and a maximum value of 100.81 ng/mL. In addition, the characteristics of intubation time were obtained with a minimum value of 2 hours, a maximum value of 11 hours, a mean of 5.93 hours, and a median of 5 hours. This is in accordance with what is stated in table 2 below.

Table 2. SP-D Levels and Intubation Time.

Patients	SP Levels=D (ng/ml)	Intubation Time (Hours)
1	21,29	9
2	8,85	7
3	75,86	11
4	72,79	3
5	95,24	5
6	11,12	2
7	35,53	8
8	24,84	5
9	17,48	2
10	8,73	2
11	26,53	9
12	54,48	6
13	37,96	3
14	100.81	4
15	38,59	11
16	8,03	2
17	82,54	4
18	99,09	5
19	24,48	5
20	19,52	9
21	12,17	4
22	91,08	5
23	17,76	3
24	23,31	8
25	49,89	7
26	15,53	9
27	11,91	9
28	94,80	9

3.2 Relationship between Serum Surfactant Protein-D (SP-D) Levels with Intubation Time in COVID-19 patients

In this study, the average level of Surfactant Protein-D (SP-D) serum was 42.15 ng/mL hour with a standard deviation of 32.71 ng/mL. If grouped based on intubation time, the average patient who had an intubation time of < 8 hours had a serum Surfactant Protein-D (SP-D) level of 45.4 ng/mL, while the average Surfactant Protein-D (SP-D) level was) serum in the group of patients who were intubated > 8 hours was 36.28 ng/mL. Statistical analysis was carried out to see the significance of Surfactant Protein-D (SP-D) serum levels on intubation time in Covid-19 patients. Prior to the correlation test, a normality test was performed to see the distribution of the data using the Shapiro-Wilk. The results of the normality test on serum surfactant levels and intubation time showed that the data were not normally distributed (p: 0.001 and p: 0.035) so the analysis was carried out using the Spearman test. The results of the analysis showed that the level of strength of the correlation between serum levels of Surfactant Protein-D (SP- D) and intubation time was 0.201 or sufficient. In addition, the analysis also showed that therewas no significant relationship between serum Surfactant Protein-D (SP-D) levels and intubation time in Covid-19 patients (p: 0.304).

3.3 Differences in Serum Surfactant Protein-D (SP-D) Levels based on Mortality

In this study, an analysis was also carried out to see differences in serum surfactant protein-D (SP-D) levels in patients who died and survived. A total of 23 patients died with a mean Surfactant Protein-D (SP-D) serum level of 37.3±29.2, while 5 patients managed to survive with an average SP- D serum level of 64.4±42.2.

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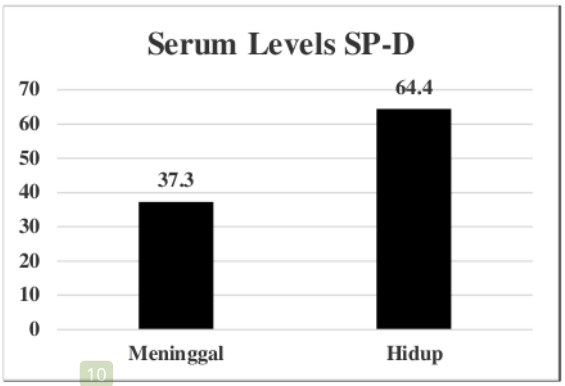

Figure 1. Diagram of Serum Surfactant Protein-D (SP-D) Levels on Mortality

The normality test according to Figure 1 shows that the data is not normally distributed so that statistical analysis was carried out using the Mann Whitney test. The results of statistical tests showed that there was no significant difference in the serum surfactant protein-D (SP-D) levels in patients who died and survived (p: 0.159).

4. DISCUSSION

4.1 Characteristics of Research Subjects

This study involved all Covid-19 patients who were tested for Serum Protein-D levels and intubated. In a retrospective data search in RES and RIK 1 RSUD Dr.Soetomo Surabaya in March to August 2020 obtained as many as 28 subjects. The data taken were patient identity, comorbidities, time of intubation, P/F ratio when intubated, serum SP-D levels, SOFA score and mortality. Age is a significant risk factor for severe COVID-19 because of the comorbidities and decreased immune system efficiency associated with normal aging. A systematic review and meta- analysis conducted by showed that patients >75 years of age had a higher risk of contracting COVID-19 (OR 2.65; 95% CI 1.81-3.90) [2]. [13] in a retrospective multicenter cohort study, found that of 625 Covid-19 patients between 10 January to 15 March 2020, the mean age was 46 years with a distribution of 329 (52.6%) were male, 37 (5.9%) were children (≦18 years), 261 (41.8%) young adults (19–44 years), 248 (39.7%) middle-aged adults (45-64 years) and 79 (12.6%) elderly adults (65 years or older). Elderly patients (≥65 years) with Covid-19 had the highest risk for severe or critical illness (33.0%, test 2 p <0.0001), intensive care (35.4%, test 2 p <0.0001), respiratory failure (31.6%, 2 test p < 0.0001) and length of hospital stay (median 21 days, Kruskal-Wallis test p < 0.0001), which may be due to a higher incidence of comorbidities and immunity. bad body against Covid-19 [13]. This is in accordance with the results of this study, there were many in the 41-50year age group and 51-60 years were the highest group affected by COVID-19. Male gender is a risk factor for severe COVID-19 disease due to a combination of sex hormone-mediated immune responses, and differences in ACE2 expression between the sexes. It was explained that women have more and stronger adaptive immune responses than men. The production of sex hormones and differences in the number of genes related to immunity were found to be higher on the X chromosome. ACE2 levels in women were higher than in men because the ACE2 gene was found on the X chromosome and tends to decrease with age. [20] from a systematic review, found that 845 (64%) men were at risk of dying from Covid-19 in China and Korea [2], [20]. The results of the previous study were similar to this study, where the number of male patients was 20 people (71.4%) more than female patients.

A high SOFA score (≧4) indicates multi-organ failure (respiratory, coagulation, hepatic, cardiovascular,

central nervous system, and renal). [20] found that a SOFA score of 4 was obtained in Covid-19 patients who died [20]. After adjusting for age, sex and comorbidities, multivariable analysis revealed a high SOFA score (hazard ratio [HR], 1.54; 95% CI 1.23–1.92; p < 0.001) and a longer time from hospital admission. illness to intubation (≥ 120 hours) (HR, 2.41; 95% CI, 1.15-5.07; p = 0.020) was an independent predictor of 28-day mortality in COVID-19 patients receiving invasive ventilation [18]. In observing the SOFA score data, the research subjects were categorized into 3, namely SOFA scores <9, 9-11, and >11. A total of 26 patients had SOFA scores <9. In addition, it was also found that the average SOFA score of patients who were intubated was 5.57 ± 2.28. In this study the PaO2/FiO2 ratio, prior to intubation, was categorized using the Berlin definition where a PaO2/FiO2 ratio <100 was included in severe ARDS and 100-200 included moderate ARDS. The PaO2/FiO2 ratio in patients was categorized into 2, namely <100 (14 patients) and 100-200 (14 patients). The average value of the PaO2/FiO2 ratio of all intubated patients was 109.34±40.66. This is because in COVID-19 patients, lung permeability increases due to inflammation. In addition, the decrease in negative intrathoracic pressure due to hypoxia causes interstitial lung edema resulting in a decrease in the value of PaO2/FiO2. In addition, in this study it was found that hypertension was the most common comorbidity suffered by patients, as many as 10 patients (35.2%). Meanwhile, the other comorbidities suffered by the next patient were diabetes mellitus, as many as 7 patients (25%). Based on research conducted by [11], [19] Covid-19 patients with hypertension were associated with outcomes, length of hospital stay, and ICU admission. Patients with Covid-19 hypertension have a two-fold higher risk of death. Like hypertension, Covid-19 patients with diabetes have a higher risk of being hospitalized and admitted to the ICU. Reported that patients with diabetes had a nearly three times higher risk of ICU admission (OR 2.79; 95% CI: 1.85-4.22) and death (OR 3.21; 95% CI: 1 ,82-5.64) [11], [19].

Diabetes is related to the progression of Covid-19 due to hyperglycaemia conditions that cause immune dysfunction, namely impaired neutrophil function, antioxidant system, and humoral immunity, and is easy to become infected with nosocomial infections that aggravate Covid-19 symptoms [4]. Therapy in hypertension, diabetes mellitus and cardiovascular disease is needed to increase the expression of ACE2 protein, in patients with Covid-19 infection, SARS- CoV-2 binds to ACE2 causing an increase in viral load and cytokine storm which in turn downregulates ACE2 and triggers ARDS to death [20].

4.2 Serum Surfactant Protein-D (SP-D) Levels of Covid-19 Patients

Serum surfactant Protein-D (SP-D) functions in lung defense and regulation of the inflammatory response. Its dysregulation in lung disease, indicated by increased serum SP-D levels caused by lung tissue damage kerusakan [6]. Quantification of absolute serum SP-D levels using an enzyme-linked immunosorbent assay (ELISA) of monoclonal antibodies against blood serum SP-D or SP-D of Broncho Alveolar Lavage Fluid (BALF) [8]. Surfactant protein-D (SP-D) is a member of the collectin subgroup of the C-type lectin superfamily. produced by type II alveolar epithelial cells. This study found that the average serum SP- D level in Covid-19 patients in the intensive room of Dr Soetomo Hospital was around 42.15 ng/ml. The criteria for severe COVID-19 cases are cases with respiratory distress (RR 30x/minute), SpO2 in room O2 93% and FiO2 300 mmHg. The decreased SP-D concentration in the blood during ARDS is due to damage to the type II alveolar epithelium due to apoptosis or necrosis, which is the site of SP- D synthesis, the effects of inflammatory mediators and bacterial toxins, a consequence of increased degradation or inhibition by proteins in the alveolar space. In addition, the greater solubility of SP-D in the alveolar fluid makes it more susceptible to proteolytic degradation [5]. The difference in SP-D levels in this study with several other studies was caused by differences in the characteristics of the subjects studied. Therefore, further research needs to be done to find out that the possibility of low serum SP-D levels in COVID-19 cases is caused by a disorder of SP-D producers, namely dysfunctional AT-2 cells.

4.3 Covid-19 Patient Intubation Time

In this study, based on intubation time, the average patient who had an intubation time of < 8 hours had a serum Surfactant Protein-D (SP-D) level of 45.4 ng/mL, while the average Surfactant Protein-D (SP-D) level was) serum in the group of patients who were intubated > 8 hours was 36.28 ng/mL. There was no significant difference in serum SP-D levels of patients intubated < 8 hours compared to patients intubated > 8 hours (p = 0.304). Acute hypoxemic respiratory failure or acute respiratory distress syndrome (ARDS) is a common and serious complication of Covid-19 infection. Approximately 12%-15% of hospitalized patients require invasive ventilation via endotracheal intubation. The goal of intubation is to quickly secure the airway and minimize aerosol formation [3]. Positive pressure from the ventilator on inspiration prevents small alveoli from collapsing [17]. Delayed tracheal intubation may negate the potential benefit of mechanical ventilation [10]. Some experts argue that mechanical ventilation should be used early to prevent the progression of COVID-19 from mild to severe. Marini and Gattinoni in the JAMA Editorial emphasized this, they proved that vigorous spontaneous inspiratory efforts lead to self-induced lung injury (P-SILI). Gattinoni advocated a radical change in the ventilator management of patients with COVID-19 so that more severe ARDS could be avoided. Mechanical ventilation saves lives in severe respiratory failure [17]. The timing of appropriate intubation and mechanical ventilation in patients with respiratory failure is complex. A study by [9] consisted of 175 patients (75.7%) receiving mechanical ventilation during their ICU stay. The median time from ICU admission to intubation was 8.1 hours (IQR, 0.3-20.1 hours). Seventy-six patients (43.4%) were intubated before (eg, in the emergency department) or within 8 hours of ICU admission, 57 (32.6%) were intubated 8 and 24 hours, and 42 (24.0%) were intubated 24 hours after admission to the ICU. The median time to intubation among patients intubated 24 hours after ICU admission was 2.3 days (IQR, 1.2–3.1 days) with a range of 1.0–8.3 days. Delayed intubation was not significantly associated with further lung injury in the study's critically ill patient population [9].

4.4 Relationship between Serum Surfactant Protein-D (SP-D) Levels with Intubation Time in COVID-19 patients

In this study, there was no significant difference in serum SP-D levels of patients who were intubated < 8 hours compared to patients who were intubated > 8 hours (p = 0.304). On the one hand, it is known that COVID-19 causes desquamation of type II pneumocytes (involved in the production of pulmonary surfactant) causing alveolar dysfunction, edema, and bleeding. ARDS patients infected with Covid-19 often show a decrease in the amount of surfactant in the lungs (higher surfactant in serum). This causes an increase in surface tension which eventually makes the alveoli tend to collapse. As a result, the entire lung collapses and volume decreases. A continuous decrease in lung volume and an increase in the volume of air into the inspiration will cause a decrease in pressure in the interstitial space which draws fluid and anti-inflammatory substances into the interstitial space causing interstitial pneumonia. Severe interstitial pneumonia is a late symptom of COVID-19 and the patient requires intubation [12]. Studies of the relationship between SP-D levels and the timing of intubation initiation in Covid-19 patients have not been found. The clinical findings of COVID-19 are broad from mild to severe in the form of ARDS, with increased levels of SP-D and other pulmonary inflammatory mediators, as well as many studies on the positive impact of intubation on ARDS patients (due to Covid-19 and other lung diseases). In this study, the average serum SP-D level was 42.15 ng/mL with a standard deviation of 32.71 ng/mL. If grouped by time of intubation, then the average serum SP-D level in the group of patients who were intubated > 8 hours was 45,4 ng/mL. 36.28 ng/mL.

4.5 Differences in Serum Surfactant Protein-D (SP-D) Levels based on Mortality

Serum Surfactant Protein-D (SP-D) levels have been shown to correlate with ARDS mortality in Covid-19 patients [16]. Based on the central role of SP-D in lung defense, regulation of the inflammatory response

and its dysregulation in lung disease, it is hypothesized that increased levels of SP-D in blood serum are caused by lung tissue damage. This is confirmed by a study comparing serum SP-D levels in 37 patients with acute respiratory distress syndrome due to H1N1 virus infection and 40 healthy controls. It was found that patients with SP-D concentrations <250 ng/mL showed an estimated 28-day survival. 0.91 (95% CI 0.51-0.98) while the probability was 0.38 (95% CI 0.16-0.61) for the SP-D group >250 ng/mL ($p < 0.021$), so higher serum SP-D levels are associated with a higher risk of death in patients with pneumonia due to H1N1virus infection [6]. In this study, the researchers did not find any difference in the serum surfactant protein-D (SP-D) levels in patients who died and who lived ($p=0.159$). The mean serum surfactant protein-D (SP-D) level in patients who died was 37.3 ng/ml, while the mean serum level of SP-D in patients who were still alive was around 64.4 ng/ml. Several things that caused the surviving patients to have higher SP-D levels in this study were the possibility that SP-D was able to bind and neutralize both gram-negative and gram-positive bacteria by acting as opsonins, where this protein induces phagocytic aggregation against bacteria. In addition, SP-D binds to the virus via the CRD domain with glycoproteins on the viral surface [7]. These results suggest that SP-D is an important biomarker of lung injury in patients with ALI/ARDS. SP-D levels may reflect type II cell hyperplasia. Instillation of intrabronchial keratinocyte growth factor, which results in type II cell hyperplasia, results in increased plasma SP-D levels. Plasma SP-D levels are elevated in early ALI/ARDS in line with increased alveolar epithelial permeability due to type II cell hyperplasia.

5. CONCLUSION

From this study it can be concluded that the examination of Surfactant Protein-D level did not show a meaningful correlation with intubation time on Covid-19 patients.

6. Funding

By self

7. Conflict Interest

There is no conflict interest in this study.

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