https://doi.org/10.48047/AFJBS.6.12.2024.4829-4837

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Mortality biomarker of mechanical ventilator-supported pneumonia patients in intensive care unit: SDC-1

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Article History
Volume 6, Issue 12, 2024
Received: 12 May, 2024
Accepted: 27 May, 2024
doi:
10.48047/AFJBS.6.12.2024.4829-4837

ABSTRACT
Background: Pneumonia mortality rate is up to 20%, while the intensive care unit (ICU) rate reaches 50%. Pneumonia mainly targets alveolar epithelial cells and the epithelial barrier which contains glycocalyx. Syndecan (SDC) is a type of proteoglycan that is found on the surface of cells and is part of the glycocalyx. The alveolar endothelium and epithelial cells exhibit the expression of SDC-1 in bronchoalveolar lavage (BAL) fluid when inflammation occurs.
Aim: This study investigates the release of SDC-1 to demonstrate the breakdown of the glycocalyx barrier in the alveolar epithelium of patients with pneumonia. Furthermore, it aims to ascertain the impact of this harm on ICU mortality.
Material and Methods: A total of 24 patients with pneumonia on mechanical ventilators in the ICU were included in this cross-sectional analytical observational study. Alveolar epithelial SDC-1 levels retrieved in BAL by fiber-optic bronchoscopy (FOB) and pneumonia severity index (PSI) scoring were assessed.
Results:Spearman's rho correlation test shows strong positive correlation between alveolar epithelial SDC-1 level and PSI score ($p < 0,001$; $r = 0,739$). However, Mann-Whitney U test shows no significant correlation between alveolar epithelial SDC-1 level and mortality in ICU ($p = 0,582$).
Conclusion: Higher alveolar epithelial SDC-1 level correlate positively with PSI score while it does not show significant correlation with ICU mortality.
Keywords:syndecan-1, Bronchoalveolar Lavage, Pneumonia Severity Index, Mortality

1. Introduction

Pneumonia is a common respiratory condition in the intensive care unit (ICU), with approximately half of patients diagnosed with the condition. The mortality rate for patients treated in the ICU ranges from 20% to 50%(Jeon et al., 2023). The prognosis of pneumonia is generally better in young adults, but older patients or those under 4 years old have a poorer prognosis. If not treated promptly, the mortality rate could escalate to 30%(Sattar et al., 2024).

The PSI (Pneumonia Severity Index) has become the established benchmark for assessing the risk of community-acquired pneumonia due to its high accuracy in predicting outcomes, as well as its effectiveness and safety(Aujesky& Fine, 2008). PSI score demonstrates more sensitivity than CURB-65 in predicting mortality rates across all age groups(Z. Zhang et al., 2018).

SDC, or Syndecan, is a type of proteoglycan found on the surface of epithelial cells. It has a role in binding and regulating different pro-inflammatory substances. The SDC (SDC-1, -2, -3, and -4) can be categorized into four varieties. SDC-1 is predominantly located on the basolateral surface of alveolar epithelial and endothelial cells, with a higher presence in epithelial cells compared to endothelium cells(Mundt et al., 2014; Park et al., 2004; Pruessmeyer et al., 2010).

Pneumonia predominantly inflicts harm onto the alveolar epithelium, specifically targeting the epithelial glycocalyx layer. Nevertheless, numerous prior investigations focused solely on elucidating the effects of pneumonia on the endothelium glycocalyx layer(Kajita et al., 2021; Murphy et al., 2017; Park et al., 2004). But there has been less study on the structure and function of the epithelial glycocalyx, particularly in relation to human subjects(Brooks &Mias, 2018; Kajita et al., 2021; Semedi et al., 2021).

The objective of this study is to evaluate SDC-1 as a biomarker for the epithelial glycocalyx in order to determine the severity of pneumonia measured by PSI score. Additionally, it seeks to analyze the effectiveness in predicting mortality in pneumonia patients who are receiving mechanical ventilation in the intensive care unit (ICU).

2. Methodology

A cross-sectional observational study was conducted in the ICU of Dr. Soetomo Hospital in Surabaya from February to April 2024. The study underwent assessment by the Ethics Committee of Dr. Soetomo Hospital and was granted approval with the reference number 0922/KEPK/II/2024 in February 19th 2024.

Using consecutive sampling, we enrolled a total of 24 pneumonia patients who were supported by mechanical ventilators. Prior agreement was obtained from the patients' family or guardian. The research subjects comprised only of ICU patients who required fiber-optic bronchoscopy (FOB). Patients with preexisting lung conditions such as COVID-19, lung tuberculosis, lung cancer, lung trauma, pneumonitis, and lung edema were not included in the study.

The PSI score was evaluated on the first day of admission to the ICU at Dr. Soetomo Hospital, using the PSI scoring system. Bronchoalveolar lavage (BAL) fluid was collected within the first three days after the indication for FOB. The BAL fluid was transferred into a 15 mL falcon tube and labeled for identification. The tube was then sealed with parafilm to ensure isolation. The tubes were placed in a styrofoam container filled with dry ice and transferred to the Clinical Pathology Laboratory at Dr. Soetomo Hospital. The quantification of SDC-1 was performed using the SDC-1 (CD138) Human ELISA method.

Table 1. PSI score calculation (Ravidranant 2016)

Factors	Score
Patients age	
Male	Age
Female	Age - 10
Long-term care facility resident	+10
Accompanying disease	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Chronic kidney disease	+10
Symptoms at diagnosis	
Acute psychosis	+20
Breathing rate ≥30/min	+20
Systolic pressure <90 mmHg	+15
Body temperature <35°C or ≥40°C	+15
Heart rate ≥125/min	+10
Laboratory measurement	
Arterial blood pH <7.35	+30
BUN ≥30 mg/dL	+20
Serum sodium <130 mEq/L	+20
Serum glucose >250 mg/dL	+10
Hb <9 mg/dL (hematocrit <30%)	+10
Atmospheric arterial blood gas (PaO_2) <60 mmHg (SaO_2 <90%)	+10

Table 2. PSI Score interpretation RAVIDRANANT

PSI Score	**Class**
0-50	I
51-70	II
71-90	III
91-130	IV
>130	V

The statistical analysis was conducted using the IBM version 24.0 of the Statistical Package for the Social Sciences (SPSS) developed by IBM Corporation in the United States. The Saphiro-Wilk test was used to perform a normality test. A Spearman analysis was conducted to assess the association between SDC-1 and the PSI score. The Mann-Whitney U test was used to establish the statistical significance of SDC-1 and mortality in the ICU.

3. Results and Discussion

Table 3. Research subject characteristic

Characteristics	n (%)	Mean ± SD
Age (years)		48,63 ± 16,92
18-20	1 (4.2%)	
21-30	5 (20.8%)	
31-40	2 (8.3%)	
41-50	3 (12.5%)	
51-60	8 (33.3%)	
≥61	5 (20.8%)	
Gender		
Male	14 (58.3%)	
Female	10 (41.7%)	
Body Mass Index (kg/m^2)		24,1 ± 3,2
≤18,50	1 (4,2)	
18,50 24,99	14 (58,3)	
25-29,9	9 (37,5	
Comorbidities		
None	3 (12,5)	
Present	21 (87,4)	
1 Comorbidity	2 (8,3)	
2 Comorbidities	7 (29,2)	
3 Comorbidities	6 (25,0)	
4 Comorbidities	2 (8,3)	
5 Comorbidities	4 (16,7)	
ICU Stay (Days)		15,04 ± 9,29
Risk Factors		
None	0 (0)	
Present	24 (100)	
1 Risk factor	4 (16,7)	
2 Risk factors	7 (29,2)	
3 Risk factors	7 (29,2)	
>3 Risk factors	6 (25)	
Antibiotic use		
Yes	24 (100)	
No	0 (0)	

Table 4. SDC-1 vs. PSI Score

Variables	Mean ± SD	p-value	r
SDC-1	1.85 ± 2,78	<0.001*	0.739
PSI Score	102.08 ± 24.18		

Patient outcome	n (%)	SDC-1 (Mean ± SD)	p-value
Survived	11 (52.3%)	1.27 ±1.68	0.582
Died	13 (61.9%)	2.33 ±3.45	

Table 5. SDC-1 vs. ICU mortality

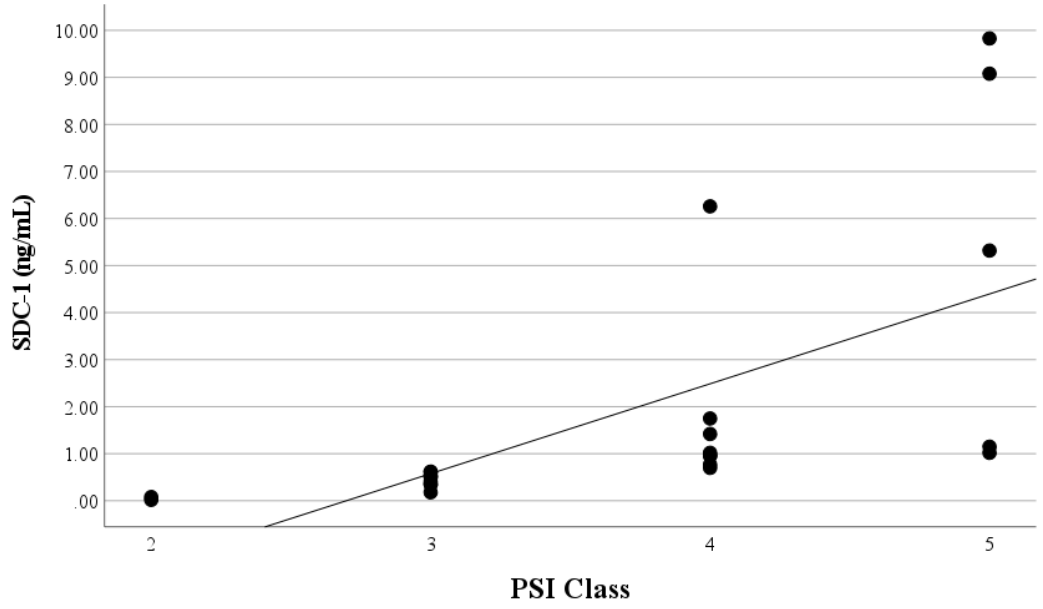

Figure 1. SDC vs. PSI score categorized by class

Currently, there is not enough evidence that definitively establishes the standard range for dissolved alveolar epithelial SDC-1 in bronchoalveolar lavage fluid, particularly in human participants(Lam et al., 2015). The reason for this is that the majority of prior studies focused on conducting experiments on animals, whereas research involving human subjects mostly investigated the impact on the endothelium glycocalyx layer(Li et al., 2021).

The review article conducted by Bertrand, et al. discovered a diverse range of concentrations of dissolved SDC-1 in samples of human body fluids spanning from 1998 to 2018(Bertrand & Bollmann, 2019). The research, carried out by Hasegawa, et al., utilized BAL fluid samples to examine individuals diagnosed with multicentric Castleman's disease (MCD)(Hasegawa et al., 2007). The study revealed an increase in the concentration of dissolved SDC-1 in the BAL fluid. The study employed different SDC-1 threshold values for BAL samples and blood serum, specifically 155 ng/mL for BAL and 450 ng/mL for serum. Additional research has identified variations in the SDC-1 cut-off values. For instance, Albert, et al. established a threshold of 30.5 ng/mL for endothelial SDC-1 in individuals with head injury(Albert et al., 2018), while Lestari, et al. utilized a cut-off value of 15.5 pg/mL for patients with pneumonia and sepsis(Lestari et al., 2020). Differences in results can be affected by demographic factors, the specific diseases being studied, the presence of other medical conditions, the methods used to select and sample participants, and the size of the sample.

Pneumonia is the main cause that increases the risk of lung injury, and its inflammatory reaction may lead to the production of alveolar epithelial SDC-1. A study conducted on mice discovered that elevating the concentration of lipopolysaccharide (LPS) results in intensified harm to the alveolar epithelium and higher amounts of soluble SDC-1 in the BAL(D. Zhang et al., 2021). This observation aligns with the outcomes of this investigation. A significant positive association was found between the increase in dissolved SDC-1 level in BAL and the severity of pneumonia, as indicated by the PSI score, in all pneumonia patients with PSI scores of degrees III, IV, and V ($p < 0.001$; $r = 0.739$).

The study discovered that there is no meaningful connection between the rise in alveolar epithelial SDC-1 levels and mortality in the ICU ($p = 0.582$). Therefore, it can be concluded that SDC-1 is not a reliable biomarker for predicting mortality. Levels of SDC-1 can elevate in chronic disorders such as heart failure, kidney failure, diabetes mellitus, acute respiratory distress syndrome (ARDS), and infectious infections including pneumonia and sepsis, which exacerbate organ failure. Furthermore, the variation in the treatment of doctors over the 3-month period of data collection may introduce a confounding factor when

evaluating mortality rates, since there may be monthly fluctuations in the composition of the ICU doctor team. Kajita, et al. discovered a correlation between elevated levels of plasma SDC-1 and the presence of ARDS(Kajita et al., 2021). They observed that lower levels of pa02/fio2 and disease severity were associated with ICU patients. However, Murphy, et al. presented evidence that refuted this idea(Murphy et al., 2017). They found that sepsis patients without lung infections had greater levels of plasma SDC-1. These findings indicate that assessing SDC-1 levels in individuals with sepsis can help identify patients who are at a heightened risk of experiencing organ failure and fatality.

Studies have documented the elevated death rate among pneumonia patients receiving treatment in intensive care. A multi-center study conducted in Europe examined the mortality rate of pneumonia patients treated in ICU, revealing a mortality incidence of 19%(Le Gall, 1993). A study conducted by Ferrer, et al. revealed that the 30-day death rate for patients receiving mechanical ventilation in the ICU was greater compared to pneumonia patients who did not require mechanical ventilation(P. S. Airlangga et al., 2022; Ferrer et al., 2018). Based on our research findings, the mortality rate within 30 days of therapy in the ICU was higher among patients who died compared to those who survived. Based on the patient data, two research subjects died within 30 days. Specifically, one subject passed away while in the ICU, while the second subject died in the treatment room after being discharged from the ICU. These variables, including advanced age, comorbidities with a high PSI score, and the presence of organ dysfunction along with preexisting comorbidities, are independently linked to death(Ferrer et al., 2018).

In addition to age, gender, and BMI,(Astuti Wulandari et al., 2022; Cillóniz et al., 2018; de Miguel-Yanes et al., 2021; López-de-Andrés et al., 2021; Nie et al., 2014) the mortality rate of persons with pneumonia is also affected by the existence of comorbidities. In a retrospective analysis undertaken by Venceslau, et al., all pneumonia patients who were hospitalised at health service centres in Portugal were examined(Hespanhol& Bárbara, 2020). The study revealed that the majority of patients who died from pneumonia had one or more comorbidities. It is believed that patients with chronic conditions exert an impact on both the occurrence of pneumonia and the rate of death(A. S. Veterini et al., 2022). Bacteremia occurs when bacteria enter the bloodstream, and it can be caused by either a weakened immune system in a specific area of the body or a weakened immune system throughout the entire body. This weakened immune system is the underlying factor that contributes to the connection between death rates and the presence or absence of other medical condition(Ruiz et al., 1999).

In this study, we categorized patients with risk factors into four groups: those with one risk factor, those with two risk factors, those with three risk factors, and those with more than three risk factors. The research subjects were selected based on certain risk factors, which included patients exhibiting diminished consciousness, individuals with GERD (gastroesophageal reflux disease), achalasia, prolonged immobility, those undergoing sedative treatment, and smokers. Among the 13 deceased research subjects, over 6 individuals had more than 3 risk variables or accounted for 25% of the total. These conditions would worsen the infection of pneumonia by causing respiratory and gastrointestinal reflex disorders(Anas et al., 2021). This increases the risk of inhaling substances into the lower respiratory tract and worsens the severity of pneumonia, leading to a higher mortality rate(Cillóniz et al., 2018; Gamache et al., 2024; Quinton et al., 2018).

4. Conclusion

SDC is the primary proteoglycan found on the surface of endothelial cells. SDC-1, specifically, is located in the outermost layer of the endothelium. It can be released into the bloodstream and urine as a biomarker of vascular integrity and endothelial injury. In cases of lung injury caused by inflammation, SDC-1 can also be found in the alveolar epithelium within the alveolar cavity. Therefore, it may be inferred that alveolar epithelial SDC-1 derived from BAL fluid may have the capability to specifically evaluate the extent of pneumonia caused by lung damage. Nevertheless, it is not a comprehensive indicator of death as there are several factors associated with organ failure and other disorders that contribute to

mortality. These factors include the existence of comorbidities and other risk factors beyond pneumonia itself, as observed in our research patients.

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Citethisarticleas:**Lamerkabel, V., Airlangga, P. S., Rehatta, N. M., Santoso, K. H., Semedi, B. P., Kriswidyatomo, P., & Lestari, P. (2024).Mortality biomarker of mechanical ventilator-supported pneumonia patients in intensive care unit: SDC-1**