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Meta-analysis

Clinical and biological markers for predicting acute respiratory distress syndrome in sepsis patients: a systematic review and meta-analysis

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ABSTRACT

Sepsis is a serious condition that occurs when a person's immune system responds excessively to an infection, causing an inflammatory reaction that damages the body's organs. One of the complications that can occur in sepsis patients is acute respiratory distress syndrome (ARDS). Sepsis and ARDS are conditions with high mortality rates, so it is important to prevent them. This study aims to determine clinical and biological markers that can be used as a reference in predicting ARDS in sepsis patients, so that prevention efforts can be carried out quickly and precisely. We performed a search in two databases (PubMed and Cochrane) for articles published between January 1, 2013 and September 30, 2023 that reported markers or predictors of ARDS in sepsis patients. Eleven studies out of the 360 articles identified, met the inclusion criteria for this review. APACHE II score (MD 0.36; 95% CI=0.15-0.56), sequential organ failure assessment score (SOFA) score (Mean difference (MD)=0.50; 95% CI=0.04-0.97), CRP (MD=0.75; 95% CI=0.46-1.04), SP-D (MD=0.70; 95% CI=0.51-0.90), and serum receptor for advanced glycation end-products (sRAGE) (MD=0.72; 95% CI=0.59-0.84) have a significant influence on the incidence of ARDS in sepsis patients. Overall, the findings of a meta-analysis that included 11 studies involving 6,623 patients showed that the APACHE II score, SOFA score, CRP, SP-D, and sRAGE showed statistically significant values.

Keywords: ARDS, Biological markers, Clinical markers, Sepsis

INTRODUCTION

Sepsis is a serious condition that occurs when a person's immune system responds excessively to an infection, causing an inflammatory reaction that damages the body's organs. This condition will develop quickly and can threaten the patient's life. Around 19 million people worldwide experience sepsis every year.[1] One of the complications that can occur in sepsis patients is ARDS. This syndrome occurs when there is severe injury to the lungs, causing breathing problems. Sepsis and ARDS are conditions that are interconnected with high mortality rates.[2] This medical issue occurs due to systemic inflammation in the body, resulting in the release of inflammatory mediators which later develops a severe lung damage.[3]

The pathophysiology of ARDS involves complex processes down to the cellular tissue level, but the exact cause of ARDS is still not known with certainty.[4] Several theories state that the ARDS process begins with damage to the walls of the alveoli and pulmonary capillaries, one

of which is sepsis. Then an inflammatory response occurs from within the body in the form of the release of cytokines and other inflammatory mediators. This will cause an increase in capillary permeability. As a result, all fluids, proteins and blood cells will leak and enter the alveoli and the elasticity of the lung tissue will decrease. This makes the lungs stiff and difficult to expand and contract when breathing.[5] The capillary endothelium and alveolar epithelial cells experience further damage due to the inflammatory process. This damage can disrupt the function of the inner lining of the lungs and worsen gas exchange disorders. But many of them.[6,7] In ARDS there are various changes in response. the body becomes inflamed and causes lung damage. Several increases in biological markers such as C-reactive protein (CRP), sRAGE, surfactant protein-D (SP-D), and angiopoietin-2 (Ang-2) can occur as the body's response to ARDS.

The increase in SP-D and sRAGE in ARDS is triggered by the impairment on the alveolar epithelium during the ARDS process. An increase in Ang-2 occurs due to damage to the alveolar endothelium and an increase in CRP is a response to significant inflammation in the lungs and body. In addition, the clinical response of sepsis patients must also be assessed when experiencing ARDS through clinical markers. Clinical assessment in patients with sepsis can use the SOFA and APACHE II score.[8]

There is a high mortality rate among ARDS patients with sepsis. In cases of ARDS, there is damage to pulmonary microcirculation, increased lung permeability, resulting in bilateral alveolar infiltrates visible on chest x-ray and arterial hypoxemia.[9,10] Approximately 30% to 40% of sepsis patients die from ARDS. The mortality rate of patients with ARDS caused by sepsis is greater than the mortality of ARDS patients with other risk factors.[11] In addition, patients who experience ARDS generally have a worse prognosis than those without ARDS. Identifying populations at high risk of experiencing ARDS in sepsis patients is very important effort to prevent the occurrence of ARDS.[12]

Having measurable clinical and biological markers is critical in identifying sepsis patients at risk for ARDS. This marker can provide additional information regarding the development of ARDS in the setting of sepsis, thereby potentially increasing patient survival rates. Early knowledge of related markers is expected to avert the development of ARDS.[13,14]

Although previous research has identified several risk factors for ARDS, there is still a lack of research regarding clinical and biological markers that can be used as predictors to predict the occurrence of ARDS in sepsis patients.[15,16] Therefore, this meta-analysis was created to identify clinical markers and biologics that can be used as a reference to predict the occurrence of ARDS in sepsis patients. Enhanced risk assessment and decision making are the main impact of this study.

METHODS

Study selection

A search for relevant studies was carried out using the PubMed and Cochrane library databases, covering the period from 1 January 2013 to 30 September 2023. The keywords used were "marker" or predictor and "ARDS" and "sepsis". The objective of this study was to identify all studies reporting clinical and biological markers in septic patients with ARDS.

Selection criteria

All studies retrieved in this search were evaluated for eligibility by three investigators. If there is a difference of opinion, further discussion will take place. Eligibility of a study for meta-analysis was based on following inclusion criteria, namely study report, adult patients (>18 years) with ARDS and sepsis, report of clinical and biological markers associated with ARDS clinical outcomes, and written in English. Studies were excluded if associated clinical and biological markers came from only 1 study.

Data extraction and quality assessment

Three investigators extracted data regarding clinical and biological markers for predicting the occurrence of ARDS in sepsis patients from selected studies for inclusion in the meta-analysis. This information includes details such as name of authors, years of publication, country, design of study, total sample, sample size, and estimated association between various clinical and biological markers to ARDS. Microsoft excel was used to record the results of all studies. Study quality was evaluated independently by three authors using the Newcastle-Ottawa scale (NCOS) designed to assess the cohort and case-control studies.

Statistical analysis

A meta-analysis was performed to determine the strength of several biological and clinical markers associated with the incidence of ARDS in sepsis patients. In each study, standard MDs in markers between groups were calculated that were relevant to the clinical outcome (groups were suggested to be those with ARDS and those without ARDS). The MD is based on the calculated MD value of the specific marker. Plots are provided for clinical and biological markers processed through meta-analysis with the STATA version 17.0 application.

RESULTS

A search of online databases identified 360 articles. After an initial search by abstract and title, 15 articles remained for full-text assessment. There were 11 articles that met the inclusion and exclusion criteria after conducting an in-depth review. The article selection steps is presented in Figure 1.

Table 1: Study characteristics.

Name of authors	Years of publication	Country	Design of study	Total sample	
				ARDS	No-ARDS
Li et al[17]	2020	China	Cohort	41	109
Iriyama et al[18]	2020	Japan	Cohort	85	509
Shi et al[19]	2022	China	Cohort	179	350
Ware et al[20]	2013	USA	Case-control	100	100
Nam et al[21]	2019	Korea	Cohort	22	103
Yang et al[22]	2022	USA	Cohort	21	90
Mikkelsen et al[23]	2013	USA	Cohort	48	730
Jones et al[24]	2019	USA	Cohort	261	411
Seethala et al[25]	2017	USA	Cohort	156	2378
Villar et al[26]	2021	Spain	Cohort	86	141
Reilly et al[27]	2018	USA	Cohort	289	414

Table 2: Quality assessment for cohort studies.

Authors	Selection	Comparability	Outcome	Overall quality
Li et al[17]	3	1	2	Good
Iriyama et al[18]	3	1	2	Good
Shi et al[19]	3	1	2	Good
Nam et al[21]	2	1	2	Fair
Yang et al[22]	3	1	2	Good
Mikkelsen et al[23]	3	2	2	Good
Jones et al[24]	3	2	2	Good
Seethala et al[25]	3	2	2	Good
Villar et al[26]	3	1	2	Good
Reilly et al[27]	3	2	2	Good

Table 3: Quality assessment for case-control studies.

Authors	Selection	Comparability	Exposure	Overall quality
Ware et al[20]	3	1	2	Good

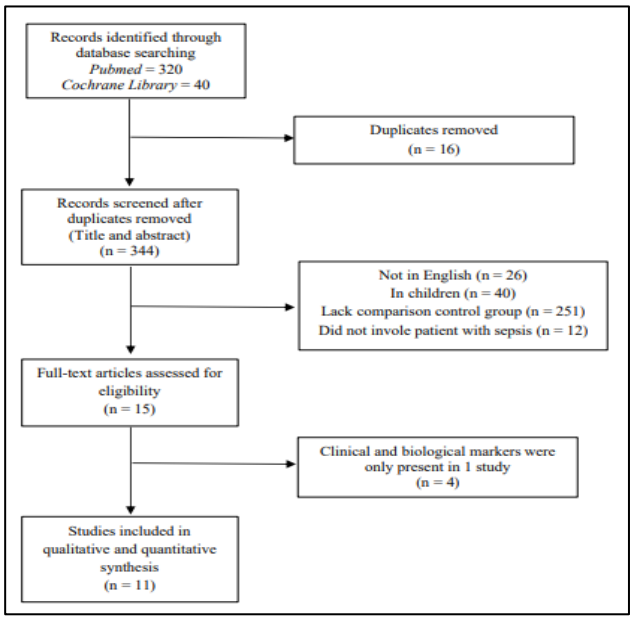

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) of article identification, screening and selection.

Predictive markers of ARDS

Surfactant protein D (SP-D)

Two studies have compared surfactant protein D (SP-D) values between case (ARDS) and control group. A higher mean SP-D score was identified in ARDS patients (MD=0.70, 95% CI=0.51, 0.90). Data from this study shows a homogeneous distribution (I-square: 0%). This marker shows significance regarding incidence of ARDS (p=0.00), as depicted in Figure 2.

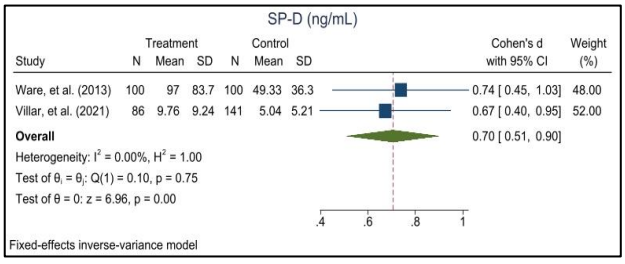

Figure 2: Impact of SP-D on the incidence of ARDS. If there is a MD >0, it indicates that the concentration of the SP-D marker is greater in ARDS patients.

sRAGE

A comparison of sRAGE values was documented in three studies. The mean sRAGE score showed an increase in patients with ARDS (MD=0.72, 95% CI=0.59, 0.84). Data from this study show a less heterogeneous distribution (I-square: 34.78%). This marker shows significance in the incidence of ARDS (p=0.00), as displayed in Figure 3.

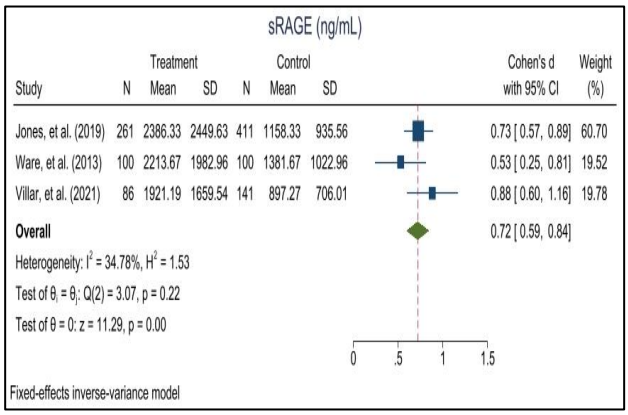

Figure 3: Impact of sRAGE on the onset of ARDS.

C-reactive protein (CRP)

Two studies have compared CRP values which identified a higher mean of CRP score in patients with ARDS (MD=0.75, 95% CI=0.46, 1.04). Data from this study shows a homogeneous distribution (I-square: 0%). This marker shows significance regarding the incidence of ARDS (p=0.00), as shown in Figure 4.

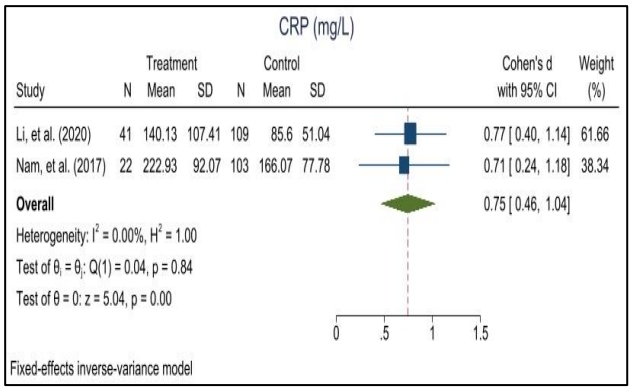

Figure 4: Impact of CRP on the incidence of ARDS.

Angiopoietin-2 (Ang-2)

Three studies have compared Ang-2 values which showed a similar mean of Ang-2 scores among ARDS patients versus the non-ARDS group (MD=0.00, 95% CI=-0.39, 0.39). Data from this study shows a homogeneous distribution (I-square: 0.10%). This marker did not show significance regarding the incidence of ARDS (p=0.99), as shown in Figure 5.

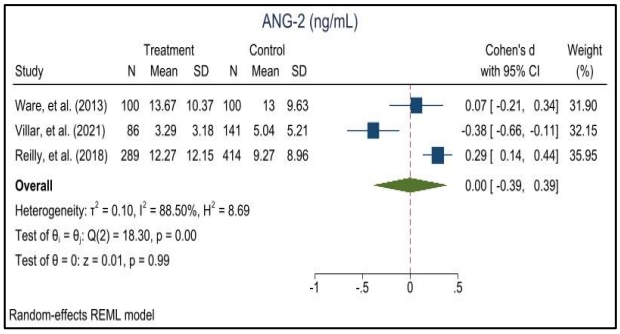

Figure 5: Impact of Ang-2 on the incidence of ARDS.

Acute physiological chronic health evaluation II score (APACHE II score)

Seven studies have evaluated APACHE II scores between patients with and without ARDS. Mean APACHE II score showed increase in ARDS patients compared with those without ARDS (MD=0.36, 95% CI=0.15, 0.56). Data from this study showed heterogeneous distribution (I-square=78.49%). This marker shows significance regarding incidence of ARDS (p=0.00) (Figure 6).

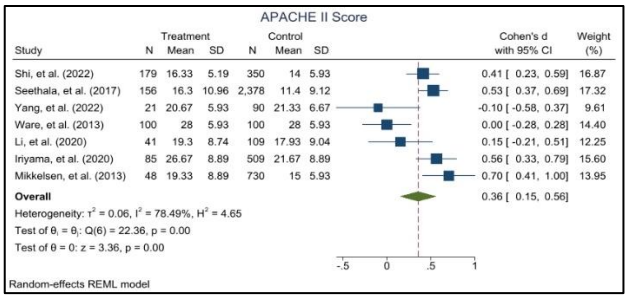

Figure 6: Impact of APACHE II score on the incidence of ARDS.

SOFA score

The mean SOFA score was higher in ARDS patients compared to those without ARDS (MD=0.50, 95% CI=0.04, 0.97). Data from this study showed a very heterogeneous distribution (I-square: 93.16%). This marker showed significance regarding the incidence of ARDS (p=0.03), as shown in Figure 7.

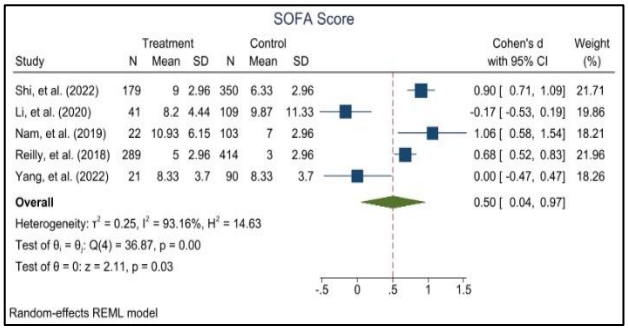

Figure 7: Impact of SOFA score on ARDS incidence.

DISCUSSION

In this study, a meta-analysis of studies reporting clinical and biological markers was carried out to determine the strength of their association with ARDS in sepsis patients, 11 studies were identified with a total of 6,623 patients with or without ARDS. In this meta-analysis, analysis was carried out on 2 clinical markers and 4 biological markers of ARDS from selected journals using the STATA application. The results of statistical analysis show significant values for several indicators such as APACHE II score, SOFA score, CRP, SP-D, and sRAGE.

The APACHE II score is an assessment method to determine the severity of the disease. Assessment using this method includes age, current medical history, examination of vital signs, and laboratory values. This method is very helpful in evaluating the patient's medical condition which will later play an important role in the type of diagnostic or therapeutic intervention required. Several previous studies have used the APACHE II score to identify patients at higher risk of developing ARDS. Apart from that, the APACHE score has a close correlation with the severity of the disease, so it can be used as an indicator in assessing the risk of ARDS in patients experiencing sepsis.[28]

A method of assessing the severity of consecutive organ failure, known as the SOFA score, is used to evaluate the level of organ failure in patients undergoing treatment in the intensive care unit (ICU). Most patients in the ICU experience conditions such as sepsis. The components contained in the SOFA score are related to certain organ functions, including respiratory function. Therefore, the SOFA score provides information about the severity of the patient's disease and the risk of developing ARDS.[29,30] One component of the SOFA score related to the respiratory system is the PaO2/FiO2 ratio, which can influence the risk of ARDS.[31,32]

CRP is a type of protein produced by the liver in response to inflammatory processes in the body. When damage occurs to the lungs, various inflammatory mediators, including cytokines, are released, triggering inflammation and stimulating CRP production in liver. CRP's function as an indicator of the inflammatory process is invaluable and helps physicians in transmitting the severity of inflammation in patients suffering from ARDS.[33,34]

Surfactant protein D (SP-D) is a type of protein produced by the lungs which plays a role in maintaining the stability of the alveolar surface and protecting the body from infections in the lungs. An increase in SP-D occurs in inflammatory conditions, one of which is caused by ARDS. Several studies show that SP-D levels can increase in patients with ARDS.[35,36]

Increased serum receptor for advanced glycation end-products (sRAGE) can be an indicator in the development of ARDS or related to the severity of ARDS events. Several studies have shown that sRAGE levels may be increased in the setting of ARDS, particularly in patients with higher ARDS severity. This shows that sRAGE plays a role in the pathological process of ARDS. Apart from that, sRAGE also has a role in reducing inflammation by binding to glycation end products which stimulate an inflammatory response, so that an increase in sRAGE can be an indicator of the body's response to inflammation in ARDS.[37,38]

CONCLUSION

Overall, the findings of this meta-analysis covering 11 studies involving 6,623 patients showed that there were two clinical markers and three biological markers that were statistically significantly associated with the incidence of ARDS in sepsis patients. These related markers include APACHE II score, SOFA score, CRP, SP-D, and sRAGE. On the other hand, the Ang-2 marker did not show statistical significance for ARDS risk. However, further research is required to identify other markers to predict the incidence of ARDS in sepsis patients, so that more markers can become potential indicators for predicting the risk of ARDS among sepsis patients.

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