Research Square

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Risk factors for developing acute respiratory distress syndrome in sepsis patients: a retrospective study from a tertiary hospital in China

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Abstract

Purpose: To investigate the risk factors for ARDS as well as for the severity of ARDS in patients with sepsis.

Methods: We retrospectively collected the characteristics of septic patients from the intensive care unit of the First Affiliated Hospital of China Medical University from January 2017 to September 2018. Logistic regression was used in determining the risk factors.

Results: 529 patients with sepsis were enrolled and 179 developed ARDS. The most common infection sites were acute abdomen (n=304) and pneumonia (n=117). Multivariate analysis showed that patients with pancreatitis and peripancreatic infection (odds ratio [OR], 3.601; 95% confidence interval [CI], 1.429 to 9.073, *P* =0.007), pneumonia (OR, 3.486; 95% CI, 1.890 to 6.430, *P<0.001*), septic shock (OR, 2.163; 95% CI, 1.429 to 3.275, *P* <0.001), a higher sequential organ failure assessment (SOFA) score (OR, 1.241; 95% CI, 1.155 to 1.333, *P* <0.001) and non-pulmonary SOFA score (OR, 2.849; 95% CI, 2.113 to 3.841, *P* <0.001) were independent risk factors for ARDS. Moreover, pneumonia is associated with increased severity of ARDS (OR, 2.512; 95% CI, 1.039 to 6.067, *P* =0.041).

Conclusions: We determined five risk factors for ARDS development in sepsis patients. Moreover, pneumonia is significantly associated with an increased severity of ARDS.

Introduction

Acute respiratory distress syndrome (ARDS) remains a major syndrome in the intensive care unit (ICU). It has been reported that 10.4% of total ICU-admitted patients develop ARDS [1]. Moreover, nearly 40% of ARDS patients are underdiagnosed [1]. Sepsis, defined as organ dysfunction induced by either pneumonia or non-pulmonary infection, is a common risk factor for the development of ARDS. Patients with sepsis-induced ARDS are reported to have a poorer prognosis than those without ARDS [2, 3] due to the lack of effective treatment strategies [4–8]. In accordance with the rapid deterioration of such clinical conditions, clinicians have shifted the management paradigm to prevent ARDS [9]. Potential risk factors for ARDS have been reported in previous studies [10–14], but there is still a lack of large-sample studies on risk factors for ARDS in ICU-admitted septic patients under the background of updated sepsis 3.0 criteria [15]. Moreover, to our knowledge, the risk factors related to the severity of ARDS in ICU sepsis patients diagnosed according to sepsis 3.0 criteria have not been reported to date.

In this study, we evaluated risk factors for ARDS and those associated with ARDS severity in patients with sepsis in ICU who were diagnosed according to sepsis 3.0 criteria.

Methods

Study population

We retrospectively collected the clinical records of adult (≥ 18 years old) patients with sepsis who were admitted to the ICU of the First Affiliated Hospital of China Medical University from Jan 1st, 2017, to Sept. 30th, 2018. Sepsis was diagnosed in accordance with the Third International Consensus Definitions for Sepsis and Septic Shock[15]. Exclusion criteria were as follows: (1). patients who underwent cardiopulmonary resuscitation (CPR); (2). patients with advanced solid or hematological tumors; (3). patients currently diagnosed with cirrhosis; (4). patients who underwent organ transplantation; and (5). patients with regular administration of hormones or immunosuppressors.

Data collection and outcomes

Clinical records were collected regarding demographic characteristics, including age, sex, underlying disease, smoking and drinking history, and site of infection of each patient. The baseline acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, SOFA score excluding respiratory function, and presence of septic shock before the development of ARDS were used to assess the severity of disease. We also included baseline laboratory data, such as PH, lactate (Lac) and serum creatinine (Scr) contents, and platelet value (PLT). The mechanical ventilation hours, length of ICU stay, length of hospital stay, and ICU mortality were recorded in detail. 28-day mortality and 90-day survival were assessed during follow up. Patients with sepsis were divided into 2 groups based on whether they developed ARDS. ARDS were diagnosed according to Berlin definition [16]. In terms of patients with ARDS, we further classified them into 3 groups based on the severity based on the oxygenation index (mild: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg, moderate: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg, severe: PaO_2/FiO_2 ≤ 100 mmHg).

Statistical analysis

All categorical variables are presented as numbers with percentages, and all continuous variables are presented as medians with interquartile ranges (IQRs). In analyzing patients with sepsis, we used the Mann-Whitney U test to compare continuous variables and the chi-square or Fisher's exact test to compare categorical variables. Logistic regression analysis was performed using covariates that were significant (P< 0.05) on univariate analysis to identify risk factors for ARDS development; a forward stepwise multivariate logistic regression model was used to screen independent predictors for ARDS development. In analyzing patients who developed ARDS, we used the Kruskal-Wallis H test to compare continuous variables and the chi-square test for categorical variables. Ordered polytomous logistic regression was used to confirm the independent risk factors for the severity of ARDS. We used IBM SPSS for Windows version 24.0 for all statistical analyses.

Results

Baseline characteristics

A total of 555 patients who met the inclusion criteria were screened, and 529 patients were enrolled (Fig. 1). The most frequent sources of sepsis site were the abdominal infection caused by the gastrointestinal

tract (n = 305), followed by the pneumonia (n = 117) and hepatobiliary system infection (n = 39). The distribution of infection sites is demonstrated in Fig. 2. The incidence of septic shock was 46%. A total of 179 (32.25%) patients developed ARDS during ICU hospitalization. The median age of ARDS patients was 66 (IQR 53–76), with 134 (74%) males. 6% had a history of drinking, and 18% had a history of smoking. Additionally, 350 (66%) of the septic patients did not develop ARDS.

According to a comparison of the patients without ARDS to sepsis-induced ARDS patients, there were significant differences in the variables including age, sex, comorbid cancer, pneumonia, acute abdominal infection caused by the gastrointestinal tract, pancreatitis with local infection, skin and soft tissue infection, septic shock, SOFA score, non-pulmonary SOFA score and APACHE II score ($P < 0.05$) (Table 1).

Comparison of prognosis between ARDS and non-ARDS patients

The median length of mechanical ventilation was 114 (IQR 46–250) hours versus 34 (IQR 13–113) hours in ARDS patients and non-ARDS patients ($P < 0.001$), respectively. The median length of stay in the ICU was 7 (IQR 4–15) days versus 4 (IQR 2-8.25) days ($P < 0.001$). Moreover, both the ICU mortality rate (23% versus 10%) and 28-day mortality (47% versus 24%) were significantly higher in the ARDS group than in the non-ARDS group ($P < 0.001$). Prognostic factor analysis results are listed in Table 2.

Risk factors for development of ARDS

Univariate analyses revealed that a total of thirteen variables (Table 1) differed significantly between ARDS patients and non-ARDS patients. We took into account the clinical significance and finally selected nine variables (sex, age, emergency admission, septic shock, pneumonia, pancreatitis, SOFA score, non-pulmonary SOFA score, and APACHE II score; Table 3) to enter into the multivariate model (Table 4). Five variables remained in the final model. Among them, pneumonia (odds ratio [OR], 3.486; 95% confidence interval [CI], 1.890 to 6.430, $P < 0.001$), pancreatitis with local infection (OR, 3.601; 95% CI, 1.429 to 9.073, $P = 0.007$), septic shock (OR, 2.163; 95% CI, 1.429 to 3.275, $P < 0.001$), SOFA score (OR, 1.241; 95% CI, 1.155 to 1.333, $P < 0.001$) and non-pulmonary SOFA score (OR, 2.849; 95% CI, 2.113 to 3.841, $P < 0.001$) were independent risk factors for development of ARDS in septic patients.

Risk factors for the severity of ARDS

Among the 179 ARDS patients, 39 (22%) were diagnosed with mild ARDS, 109 (61%) were diagnosed with moderate ARDS and 31 (17%) were diagnosed with severe ARDS. Variables that showed significant differences between ARDS and non-ARDS patients were included in the comparison among the three groups with different severities of ARDS. As a result, patients with pneumonia (mild ARDS vs moderate ARDS vs severe ARDS, 15% vs 24% vs 55%, $P < 0.001$) and higher SOFA score (7.92 vs 9.35 vs 9.58, $P = 0.014$) were more likely to develop severe ARDS. On the contrary, acute abdomen infection was the main cause of mild and moderate ARDS compared to severe ARDS (62% vs 51% vs 26%, $P = 0.010$) (Table 5). Prognostic test results showed significant differences in 28-day mortality rate (mild ARDS vs moderate ARDS vs severe ARDS, 25.6% vs 42.2% vs 41.9%, $P = 0.023$) and 90-day mortality rate (30.8% vs 43.1% vs

61.3%, $P = 0.038$) among the three groups (Table 6). Ordinal multivariate logistic regression revealed that patients with pneumonia (OR, 2.512; 95% CI, 1.039 to 6.067; $P = 0.041$) had significant correlation with increased severity of ARDS (Fig. 3).

Prognosis of pulmonary ARDS

We further analyzed the prognostic profile of ARDS patients between pneumonia and non-pulmonary infection. Significant differences were found in length of mechanical ventilation (170 hours vs 105.5 hours, $P = 0.013$), length of ICU stay (11 days vs 7 days, $P = 0.007$), ICU mortality rate (39.6% vs 16.7%, $P = 0.001$), 28-day mortality rate (62.3% vs 33.3%, $P < 0.001$) and 90-day mortality rate (64.2% vs 34.9%, $P < 0.001$) (Table 7).

Discussion

ARDS remains a difficult clinical syndrome with high morbidity and mortality in the ICU. Risk factors for ARDS have long been discussed by clinicians, but there is no consensus yet. Moreover, little is known about the direct risk factors correlating with the severity of ARDS in ICU-admitted septic patients diagnosed according to sepsis 3.0 criteria. Our study reported the incidence of ARDS in septic patients was 34%, ranking as the highest incidence rate in the literature worldwide [10–14]. Possible reasons include: (1) the increased severity of sepsis in our cohort, as 46% patients developed septic shock, which is also a higher rate than that in previous studies [17]; (2). the improved clinical recognition of ARDS at our center. We believe that our data were convincing because the 28-day mortality rate agreed with that in a previous study [13].

Our study found a younger median age in patients with sepsis-induced ARDS. Ageing is a strong risk factor for adverse outcomes in the processes of many diseases. Studies on severe sepsis or septic shock patients have shown that older (> 65), critically ill surgical patients have a higher incidence of organ dysfunction and adverse outcomes [18]. According to our results, the median age was 66 years in ARDS patients and 70 years in non-ARDS patients. There was a significant difference between the two groups. We noticed that the results of 3 studies, including ours, showed that septic patients who developed ARDS were younger than those who did not ($P < 0.05$), although age was not an independent factor for developing ARDS [10, 11]. This divergence may be due to none of the 3 studies dividing patients according to age. Instead, we compared the median ages of patients from the ARDS group and non-ARDS group. Another possible reason is that ARDS is a clinical condition characterized by severe inflammatory responses accompanied by immune activation [19]. A set of functional and structural alterations in the immune system has been considered a crucial component of aging, such as a diminished response to vaccination and decreased inflammation grade [20]. This diminished response might be the underlying reason why ARDS patients had a younger median age than non-ARDS patients. Further studies may focus on this interesting clinical phenomenon in critically ill patients.

Our study reported a significantly worse prognosis of patients with sepsis-induced ARDS compared with those without ARDS, regarding to the length of mechanical ventilation, length of ICU stays, and 28-day

mortality, which is in consistent with the data in the literature. Researchers reported that sepsis-associated ARDS leads to a prolonged recovery of patients from lung injury and a slower rate of extubating [21, 22] Moreover, the progression to ARDS is associated with an increased risk of in-hospital mortality in patients with sepsis. [23, 24] That's why it is at urgent need in determining risk factors for sepsis patients who develop ARDS.

We confirmed five independent risk factors for developing ARDS in patients with sepsis, including septic shock, pneumonia, pancreatitis with local infection, increased SOFA score and extrapulmonary SOFA score. Septic shock is a severe form of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase the risk of mortality. Septic shock has long been recognized as a trigger of acute lung injury (ALI) and ARDS [14]. *Iscimen et al* reported that 44% of septic shock patients developed ALI in their ICU [14], which is almost the same as the rate in our ICU (48.6%). The results from our cohort showed that septic shock is an independent risk factor for developing ARDS in septic patients, which is in agreement with a previous study [10, 11].

Apart from septic shock, we confirmed two sites of infection including pneumonia and local pancreatic infection were associated with the occurrence of ARDS. Pneumonia has been reported as the most common source of infection in patients with ARDS and a risk factor in developing ARDS [25, 26]. The direct lung damage caused by pneumonia and the indirect lung damage caused by the systemic inflammatory response of sepsis together lead to the occurrence of ARDS. Acute severe pancreatitis may be caused by hyperlipidemia, alcohol consumption or cholelithiasis. The early stage of pancreatitis is considered as an asepsis condition. We carefully reviewed the medical records and confirmed that the 25 patients with local pancreatic infection enrolled in our study developed peripancreatic infection before ARDS occurred. It has been reported that 29%-39% of pancreatitis patients developed fatal lung complications, including ARDS [27, 28]. In pancreatitis patients, the development of ARDS is believed as a consequence of severe systemic inflammatory response with increased endothelial and epithelial barrier permeability, with leakage of a protein-rich exudate into the alveolar space and interstitial tissues, thus compromising oxygenation and gas exchange [29–31]. The result of our study contributes to the literature the strong relationship between infection site and ARDS development in patients with sepsis.

The lung injury prediction score (LIPS), early acute lung injury (EALI) score, APACHE II score and SOFA score are all considered to be related to the occurrence and development of ARDS in some studies. Research targeting patients in the emergency department consistently showed that the APACHE II score is an independent risk factor for ARDS in patients with sepsis [10, 23], while our results presented a significant difference in only the APACHE II score between the 2 groups of patients, but it was not an independent risk factor for ARDS development. Conversely, the SOFA score and non-pulmonary SOFA score were calculated as risk modifiers for ARDS. As the SOFA score increases, the risk of developing ARDS in sepsis patients is higher. This result is consistent with another study in ICU-admitted bacteremia patients [12]. This phenomenon may be explained by the fact that patients admitted to the emergency department are at their early stage of the disease process, and most of them have not yet been complicated with organ failure, while ICU patients have already developed complex organ dysfunction.

This point may remind clinicians to pay more attention to respiratory function in patients with other organ dysfunction, such as acute kidney injury and dysfunction of the coagulation system.

As for clinical and prognostic factors of ARDS at different severity, our results showed patients with pneumonia and higher SOFA score were more likely to have severe ARDS. Moreover, they have significant worse 28-day and 90-day mortality rate. This result is in consistent with the mortality rate reported when ARDS Berlin Definition was published, which again illustrates the credibility of the patients enrolled in this study.[16] In addition, to the best of our knowledge, we determined for the first time that pneumonia has a significant correlation with increased severity of ARDS in patients with sepsis. Moreover, patients with pneumonia-induced ARDS showed significant worse PaO_2/FiO_2 index, longer duration of mechanical ventilation, and higher mortality rate. As we mentioned before, our results were consistent with previous studies that reported pneumonia as a risk factor in ARDS development in sepsis patients. When conquering infection, pulmonary defense system can trigger immune responses to microbes resulting in profound local and systematic inflammation, thus might develop ARDS.[32, 33] *Nam H* et al reported a significant higher proportion of pneumonia patients in 28-day non-survivors who diagnosed with ARDS caused by bacteremia-induced sepsis in Korea.[11] However, other studies showed that there is no relationship between pneumonia and increased mortality. [25, 34, 35]. Indeed, these results may not be directly comparable because of different inclusion criteria. Moreover, this might be due to the different populations between the studies, e.g., Asian, and non-Asian. We hypothesize that beneficial measurements and interventions should be implemented more aggressively in pneumonia patients to reduce the progression to severe ARDS, which may enhance the prognosis of ARDS caused by pulmonary sepsis.

ARDS is a clinical syndrome with a high rate of under-diagnosis. Up to 40% of ARDS patients cannot be clinically recognized quickly enough [1]. A better understanding of risk factors for ARDS in sepsis patients can help improve the ability of clinicians to recognize ARDS as early as possible. Moreover, several studies have shifted the emphasis from clinical risk factors to biomarkers for ARDS incidence, which is also a strategy for better precision medicine in ARDS. [36–38] Larger sample studies should be carried out to provide appropriate interventions to specific patients.

The limitations of this study are the following. 1. Our study is a retrospective study, and the homogeneity of the data is not guaranteed, which may affect the study results. 2. The severity of the disease in the selected population is high, and it cannot represent the clinical characteristics of all patients with sepsis and ARDS. 3. This study is a single-center study, and the research results cannot be extended to all patients with sepsis and ARDS or all severe patients.

Conclusion

Our study in the northeastern region of China showed that pneumonia, pancreatitis with local infection, septic shock, SOFA score and non-pulmonary SOFA score are independent risk factors for sepsis patients developing ARDS. In addition, pneumonia is significantly related to an increased severity of ARDS and

increased mortality. Multicenter, prospective studies are needed to better recognize this severe clinical syndrome with high heterogeneity.

Declarations

Ethics approval and consent to participate

The study was approved by Ethics Committee of the First Affiliated Hospital of China Medical University. All the patients or their family who enrolled in this study have signed an informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and material

The data could be shared if readers contact the authors and explain why they would like to access the data and material. Corresponding author should be contacted if someone wants to request the data from this study.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

Y Shi and X Li contributed the conception of the study, data collection and they drafted the manuscript together; L Wang contributed significantly to statistical analysis; S Yu helped to collect data. X Ma also contributed the conception of the study.

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References

1. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF *et al*: **Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries**. JAMA 2016, **315**(8):788–800.

2. Estenssoro E, Dubin A, Laffaire E, Canales H, Saenz G, Moseinco M, Pozo M, Gomez A, Baredes N, Jannello G *et al*: **Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome**. Crit Care Med 2002, **30**(11):2450–2456.
3. Cochi SE, Kempker JA, Annangi S, Kramer MR, Martin GS: **Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013**. Ann Am Thorac Soc 2016, **13**(10):1742–1751.
4. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome**. N Engl J Med 2000, **342**(18):1301–1308.
5. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT, National Heart L, Blood Institute ACTN: **Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome**. N Engl J Med 2004, **351**(4):327–336.
6. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Jr., Hite RD *et al*: **Comparison of two fluid-management strategies in acute lung injury**. N Engl J Med 2006, **354**(24):2564–2575.
7. Martinez O, Nin N, Esteban A: **[Prone position for the treatment of acute respiratory distress syndrome: a review of current literature]**. Arch Bronconeumol 2009, **45**(6):291–296.
8. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM *et al*: **Neuromuscular blockers in early acute respiratory distress syndrome**. N Engl J Med 2010, **363**(12):1107–1116.
9. Gong MN, Thompson BT: **Acute respiratory distress syndrome: shifting the emphasis from treatment to prevention**. Curr Opin Crit Care 2016, **22**(1):21–37.
10. Seethala RR, Hou PC, Aisiku IP, Frendl G, Park PK, Mikkelsen ME, Chang SY, Gajic O, Sevransky J: **Early risk factors and the role of fluid administration in developing acute respiratory distress syndrome in septic patients**. Ann Intensive Care 2017, **7**(1):11.
11. Nam H, Jang SH, Hwang YI, Kim JH, Park JY, Park S: **Nonpulmonary risk factors of acute respiratory distress syndrome in patients with septic bacteraemia**. Korean J Intern Med 2019, **34**(1):116–124.
12. Iriyama H, Abe T, Kushimoto S, Fujishima S, Ogura H, Shiraishi A, Saitoh D, Mayumi T, Naito T, Komori A *et al*: **Risk modifiers of acute respiratory distress syndrome in patients with non-pulmonary sepsis: a retrospective analysis of the FORECAST study**. J Intensive Care 2020, **8**:7.
13. Li S, Zhao D, Cui J, Wang L, Ma X, Li Y: **Prevalence, potential risk factors and mortality rates of acute respiratory distress syndrome in Chinese patients with sepsis**. J Int Med Res 2020, **48**(2):300060519895659.
14. Iscimen R, Cartin-Ceba R, Yilmaz M, Khan H, Hubmayr RD, Afessa B, Gajic O: **Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study**. Crit Care Med 2008, **36**(5):1518–1522.

15. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *JAMA* 2016, **315**(8):801–810.
16. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: **Acute respiratory distress syndrome: the Berlin Definition**. JAMA 2012, **307**(23):2526–2533.
17. SepNet Critical Care Trials G: **Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study**. Intensive Care Med 2016, **42**(12):1980–1989.
18. Brakenridge SC, Efron PA, Stortz JA, Ozrazgat-Baslanti T, Ghita G, Wang Z, Bihorac A, Mohr AM, Brumback BA, Moldawer LL *et al*: **The impact of age on the innate immune response and outcomes after severe sepsis/septic shock in trauma and surgical intensive care unit patients**. J Trauma Acute Care Surg 2018, **85**(2):247–255.
19. Kumar V: **Pulmonary Innate Immune Response Determines the Outcome of Inflammation During Pneumonia and Sepsis-Associated Acute Lung Injury**. Front Immunol 2020, **11**:1722.
20. Sadighi Akha AA: **Aging and the immune system: An overview**. J Immunol Methods 2018, **463**:21–26.
21. Dvorscak MB, Lupis T, Adanic M, Saric JP: **[Acute Respiratory Distress Syndrome and Other Respiratory Disorders in Sepsis]**. Acta Med Croatica 2015, **69**(3):167–175.
22. Sheu CC, Gong MN, Zhai R, Chen F, Bajwa EK, Clardy PF, Gallagher DC, Thompson BT, Christiani DC: **Clinical characteristics and outcomes of sepsis-related vs non-sepsis-related ARDS**. Chest 2010, **138**(3):559–567.
23. Mikkelsen ME, Shah CV, Meyer NJ, Gaieski DF, Lyon S, Miltiades AN, Goyal M, Fuchs BD, Bellamy SL, Christie JD: **The epidemiology of acute respiratory distress syndrome in patients presenting to the emergency department with severe sepsis**. Shock 2013, **40**(5):375–381.
24. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H, 3rd, Hoth JJ, Mikkelsen ME, Gentile NT *et al*: **Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study**. Am J Respir Crit Care Med 2011, **183**(4):462–470.
25. Sheu CC, Gong MN, Zhai R, Bajwa EK, Chen F, Thompson BT, Christiani DC: **The influence of infection sites on development and mortality of ARDS**. Intensive Care Med 2010, **36**(6):963–970.
26. Fujishima S, Gando S, Daizoh S, Kushimoto S, Ogura H, Mayumi T, Takuma K, Kotani J, Yamashita N, Tsuruta R *et al*: **Infection site is predictive of outcome in acute lung injury associated with severe sepsis and septic shock**. Respirology 2016, **21**(5):898–904.
27. Gliedman ML, Bolooki H, Rosen RG: **Acute pancreatitis**. Curr Probl Surg 1970:1–52.
28. Ranson JH, Roses DF, Fink SD: **Early respiratory insufficiency in acute pancreatitis**. Ann Surg 1973, **178**(1):75–79.
29. Shields CJ, Winter DC, Redmond HP: **Lung injury in acute pancreatitis: mechanisms, prevention, and therapy**. Curr Opin Crit Care 2002, **8**(2):158–163.

30. Jacobs ML, Daggett WM, Civette JM, Vasu MA, Lawson DW, Warshaw AL, Nardi GL, Bartlett MK: **Acute pancreatitis: analysis of factors influencing survival**. Ann Surg 1977, **185**(1):43–51.
31. Raghu MG, Wig JD, Kochhar R, Gupta D, Gupta R, Yadav TD, Agarwal R, Kudari AK, Doley RP, Javed A: **Lung complications in acute pancreatitis**. JOP 2007, **8**(2):177–185.
32. Delclaux C, Azoulay E: **Inflammatory response to infectious pulmonary injury**. Eur Respir J Suppl 2003, **42**:10s-14s.
33. Zhang P, Summer WR, Bagby GJ, Nelson S: **Innate immunity and pulmonary host defense**. Immunol Rev 2000, **173**:39–51.
34. Sevransky JE, Martin GS, Mendez-Tellez P, Shanholtz C, Brower R, Pronovost PJ, Needham DM: **Pulmonary vs nonpulmonary sepsis and mortality in acute lung injury**. Chest 2008, **134**(3):534–538.
35. Luo L, Shaver CM, Zhao Z, Koyama T, Calfee CS, Bastarache JA, Ware LB: **Clinical Predictors of Hospital Mortality Differ Between Direct and Indirect ARDS**. Chest 2017, **151**(4):755–763.
36. Zheng F, Pan Y, Yang Y, Zeng C, Fang X, Shu Q, Chen Q: **Novel biomarkers for acute respiratory distress syndrome: genetics, epigenetics and transcriptomics**. Biomark Med 2022.
37. Spadaro S, Park M, Turrini C, Tunstall T, Thwaites R, Mauri T, Ragazzi R, Ruggeri P, Hansel TT, Caramori G *et al*: **Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine**. J Inflamm (Lond) 2019, **16**:1.
38. Ware LB, Koyama T, Zhao Z, Janz DR, Wickersham N, Bernard GR, May AK, Calfee CS, Matthay MA: **Biomarkers of lung epithelial injury and inflammation distinguish severe sepsis patients with acute respiratory distress syndrome**. Crit Care 2013, **17**(5):R253.

Tables

Table 1. Comparisons of baseline characteristics between ARDS and non-ARDS patients.

Characteristic	ARDS（N=179）	Non-ARDS （N=350）	*P* value
Sex,（male/female）	134 (75%)/ 45 (25%)	230 (66%)/ 120 (34%)	**0.019**
Age, yr	66（53, 76）	70（60, 78）	**0.003**
History of drinking	10（6%）	27（8%）	0.236
History of smoking	32（18%）	50（14%）	0.170
Comorbidities			
COPD	7 （4%）	17（5%）	0.296
HTN	67（37%）	120（34%）	0.267
CHD	32（18%）	79（23%）	0.126
DM	37（21%）	70（20%）	0.470
Cancer	32（18%）	90（26%）	**0.026**
CKD	12（7%）	25（5%）	0.504
Hematological disorder	1（1%）	2（1%）	0.734
Infection site			
Pulmonary/Non-pulmonary	53 (30%)/ 126 (70%)	64 (18%)/ 286 (82%)	**0.002**
Pancreatitis with local infection	16 (9%)	9 (3%)	**0.002**
Acute abdominal infection caused by gastrointestinal tract	82 (46%)	222 (63%)	**<0.001**
Hepatobiliary system	18 (10%)	21 (6%)	0.067
Urinary tract	7 (4%)	19 (5%)	0.296
Skin and soft tissue	1 (1%)	12 (3%)	**0.034**
Central nervous system	0 (0%)	2 (1%)	0.437
Pleural	2 (1%)	0 (0%)	0.114
CRBSI	0 (0%)	1 (0%)	0.663
Emergency admission	87 (49%)	213 (61%)	**0.004**
Septic shock	118 (66%)	125 (36%)	**<0.001**
APACHE II	16 (13, 20)	14 (10, 18)	**<0.001**
SOFA	9 (7, 11)	7 (4, 8)	**<0.001**

Non-pulmonary SOFA	6 (4, 8)	5 (3, 6)	**<0.001**

Values are presented as median (interquartile range) or number (%).

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; HTN, hypertension; CHD, coronary heart disease; DM, Diabetes mellitus; CKD, chronic kidney disease; CRBSI, catheter related bloodstream infection; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Table 2. Prognostic analysis between ARDS and non-ARDS patients

Variable	ARDS（N=179）	Non-ARDS（N=350）	*P value*
Length of mechanical ventilation (hour)	114（45.5, 230）	34.2（13, 113）	**<0.001**
Length of ICU stay (days)	7（4, 15）	4（2, 8.25）	**<0.001**
Length of ICU stay for survived patients (days)	8（5, 15.5）	4（2, 7.75）	**<0.001**
ICU mortality（%）	23%	10%	**<0.001**
28-day mortality（%）	47%	24%	**<0.001**

ARDS, acute respiratory distress syndrome; ICU, department of intensive care unit;

Table 3. Univariate analysis of risk factors for ARDS

Variable	OR （95% CI）	*P* value
Gender	1.554 （1.038-2.326）	0.032
Age	0.990 （0.984-0.997）	0.003
Emergency admission	0.676 （0.420-0.869）	0.004
Pancreatitis and local infection	3.719 （1.609-8.595）	0.002
Pneumonia	1.880 （1.235-2.861）	0.002
Septic shock	3.482 （2.385-5.084）	<0.001
APACHE II	1.029 （1.016-1.042）	<0.001
SOFA	1.150 （1.115-1.186）	<0.001
Non-pulmonary SOFA	1.092 （1.059-1.125）	<0.001

ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; APACHEII, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment;

Table 4. Multivariate analysis of risk factors for ARDS

	OR（95% CI）	*P value*
Pneumonia	3.486 （1.890-6.430）	**<0.001**
Pancreatitis and local infection	3.601 （1.429-9.073）	**0.007**
Septic shock	2.163 （1.429-3.275）	**<0.001**
SOFA	1.241 （1.155-1.333）	**<0.001**
Non-pulmonary SOFA	2.849 （2.113-3.841）	**<0.001**

Table 5. Comparisons of characteristics between mild, moderate, and severe ARDS patients

Variables	Mild (N=39)	Moderate (N=109)	Severe (N=31）	*P value*
Sex,（male/female）	31 (79%)/ 8(21%)	80 (73%)/ 29 (27%)	23 (74%)/ 8 (26%)	0.781
Age, yr	63.18±19.28	64.30±14.69	60.68±16.19	0.538
History of drinking	6（15%）	22（20.2%）	4（12.9%）	0.595
History of smoking	2（5%）	8（7%）	0（0%）	0.274
Infection site				
Pulmonary/Non-pulmonary	6 (15%)/ 33 (85%)	26 (24%)/ 83 (76%)	17 (55%) /14 (45%)	**<0.001**
Pancreatitis with local infection	5（13%）	11（10%）	2（7%）	0.684
Acute abdominal infection caused by gastrointestinal tract	24（62%）	55（51%）	8（26%）	**0.010**
Emergency admission	26 (67%)	52 (48%)	9 (29%)	**0.007**
Septic shock	24（62%）	72（66%）	22（77%）	0.720
APACHE II	16.21±5.57	16.94±6.59	18.65±7.26	0.283
SOFA	7.92±2.65	9.35±3.06	9.58±2.88	**0.014**
Non-pulmonary SOFA	5.41±2.60	6.28±2.84	5.94±2.90	0.251

Table 6. Prognostic factors between mild, moderate and severe ARDS patients

Variables	Mild (N=39)	Moderate (N=109)	Severe (N=31)	*P value*
Mechanical ventilation time (hour)	144(49, 235)	112(44, 224)	106(48, 236)	0.861
Length of ICU stay (days)	8(3, 13)	7(4, 15)	6(3, 16.5)	0.772
Length of hospital stay (days)	19(12, 28)	22(13, 38)	24(6, 31)	0.356
ICU mortality rate	17.9%	25.7%	22.6%	0.616
28-day mortality rate	25.6%	42.2%	41.9%	**0.023**
90-day mortality rate	30.8%	43.1%	61.3%	**0.038**

Table 7. Baseline characteristics and outcome between pulmonary and non-pulmonary groups in sepsis-associated ARDS

Variable	Pulmonary ARDS (n=53)	Non-pulmonary ARDS (n=126)	*P value*
Sex(female/male)	14/39	31/95	0.799
Age(yrs)	70(55, 80)	64(53, 72.75)	**0.017**
History of smoking	14(26.4%)	18(14.3%)	0.130
Septic shock	39(73.6%)	79(62.7%)	0.161
APACHEII Score	17(13, 22)	15.5(12, 20)	0.063
SOFA Score	10(7, 12)	9(7.25, 11)	0.158
PaO_2/FiO_2	126.0(90, 167.5)	171.525(137.26, 202.25)	**<0.001**
Length of mechanical ventilation (hrs)	170 (46, 375)	105.5(40.25, 203.5)	**0.013**
Length of ICU stay (days)	11(4, 27)	7(4, 12)	**0.007**
Length of hospital stay (days)	27(12, 40)	20(12, 32)	0.082
ICU mortality	21(39.6%)	21(16.7%)	**0.001**
Hospital mortality	21(39.6%)	22(17.5%)	**0.002**
28-day mortality	33(62.3%)	42(33.3%)	**<0.001**
90-day mortality	34(64.2%)	44(34.9%)	**<0.001**

Figures

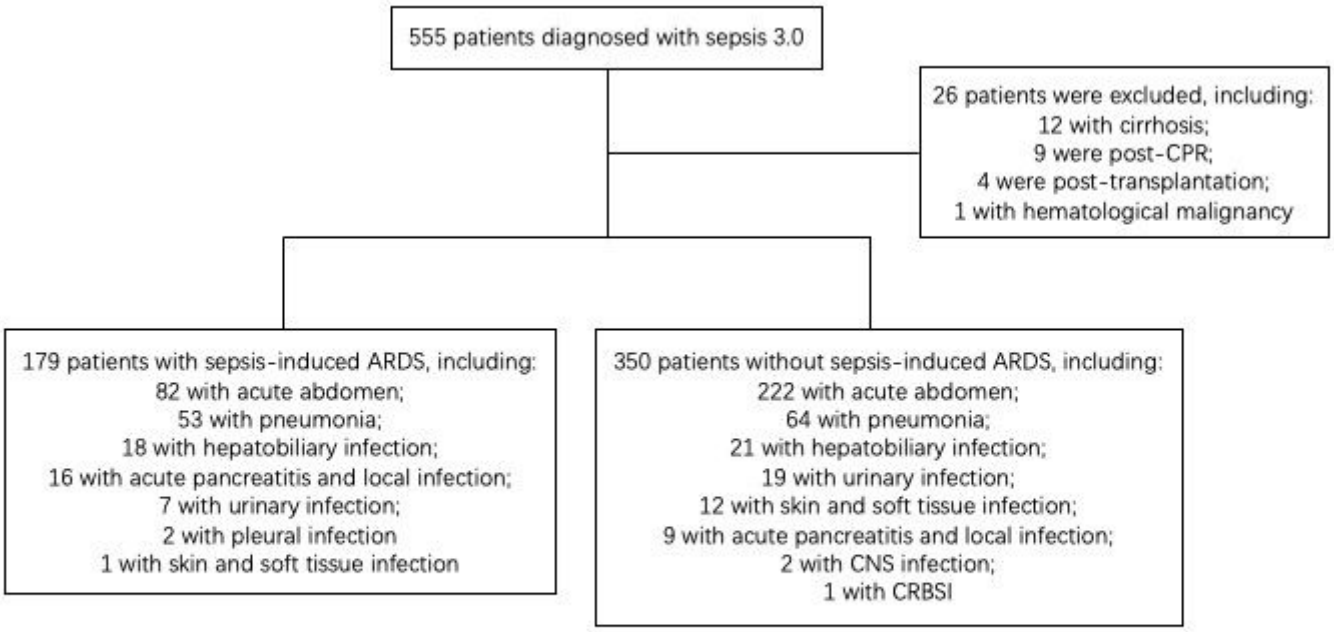

Figure 1

Flow chart of patient's who were enrolled in this study.

CPR, cardiopulmonary resuscitation; ARDS, acute respiratory distress syndrome; CNS, central nervous system; CRBSI, catheter related blood stream infection.

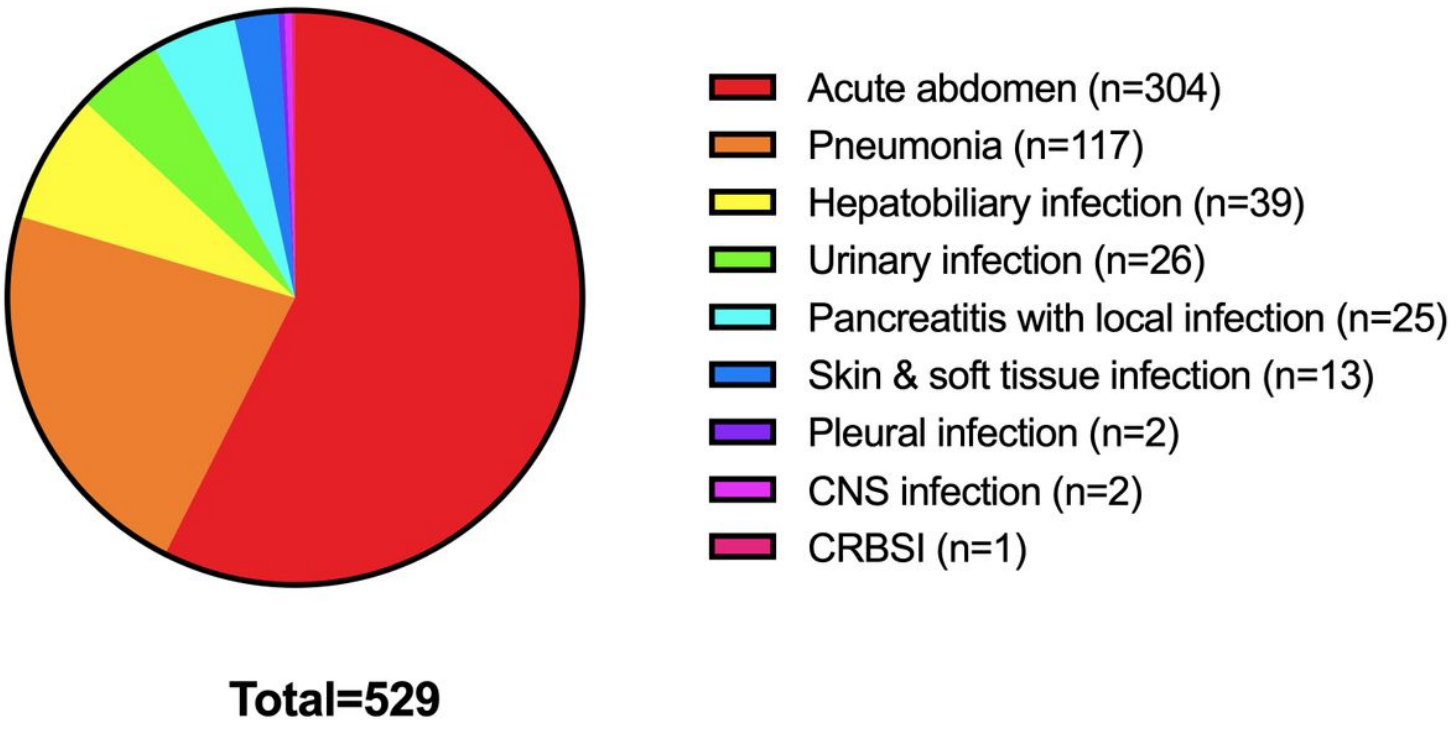

Figure 2

Distribution of infection site of sepsis patients.

CNS, central nervous system; CRBSI, catheter related blood stream infection.

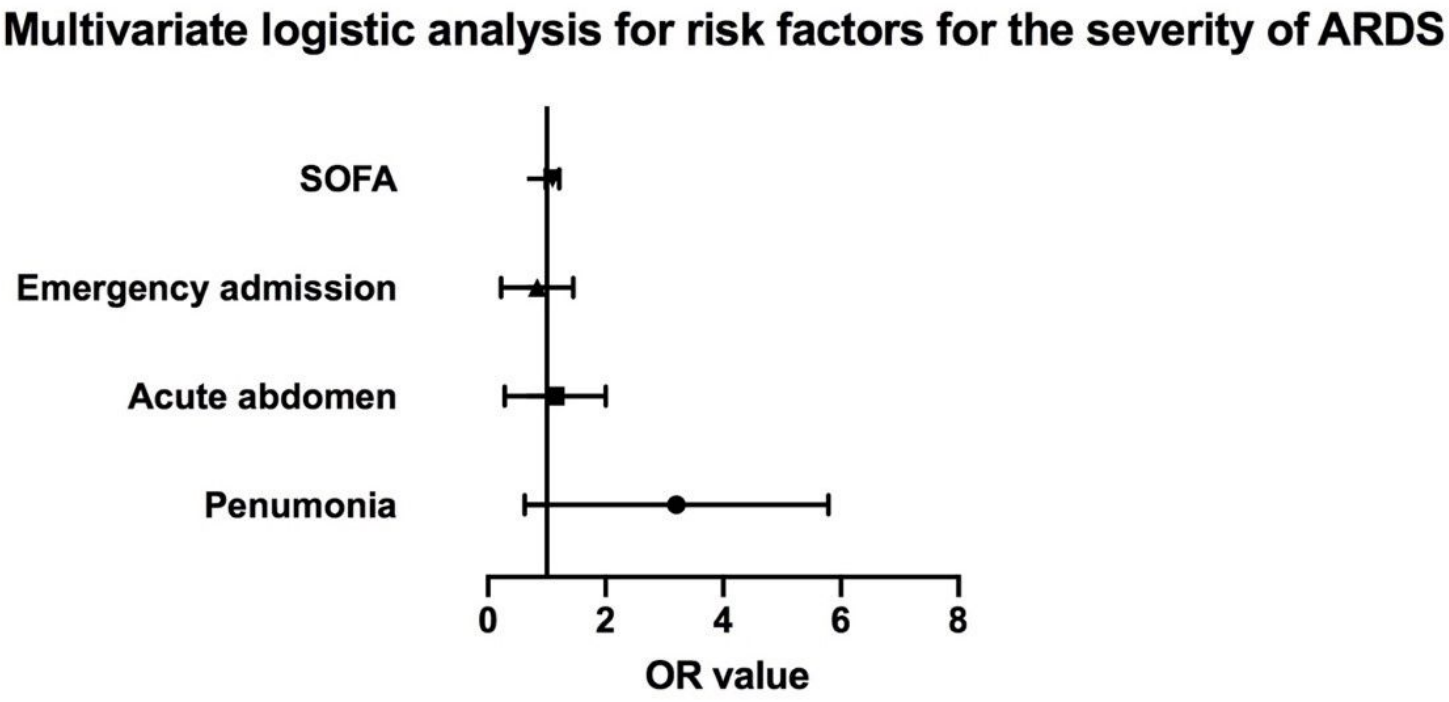

Figure 3

Forest plot for risk factors of the severity of ARDS. Pneumonia remains the only significant risk factor for increased severity of ARDS in patients with sepsis (OR 2.512, 95%CI 1.039-6.067, p=0.041). Other risk factors enrolled in the analysis include emergency admission (OR, 0.685, 95%CI 0.311-1.513, p=0.349), acute abdomen (OR, 0.926, 95%CI 0.411-2.088, p=0.852), SOFA (OR, 1.093, 95%CI 0.985-1.212, p=0.093).