REVIEW ARTICLE

Prognostic Factors of Severe Pneumonia in Adult Patients: A Systematic Review

Yanliang Yang, BM; Qianying Wang, BM; Zhiwei Yu, MM

ABSTRACT

Objectives • This systematic review aimed to identify independent prognostic factors of severe pneumonia.

Methods • A systematic search was undertaken in Pubmed, Embase, and Web of Science from inception to March 2023 to find cohort studies investigating the association between prognostic factors and adverse outcomes of severe pneumonia in adult patients. The study selection process involved screening the title and abstract of articles to identify relevant studies on severe pneumonia in adult patients. Inclusion criteria included studies with a prospective or retrospective longitudinal design, investigating prognostic factors, and performing multivariate analysis. Exclusion criteria included non-English or non-Chinese studies, studies focusing on severe pneumonia in children, studies conducting only univariate analysis, and conference abstracts, reviews, and case reports. The risk of bias was assessed by the Quality In Prognosis Studies (QUIPS) tool.

Results • A total of 27 published studies, including both prospective and retrospective cohort studies, were included. These studies reported on 53 different prognostic factors and covered four unique outcomes. The quality assessment indicated that 59.3% of the studies had a low risk of bias. Age, functional dependence, heart rate, and oxygen saturation/respiratory rate index were found to be associated with mortality. Additionally, various laboratory indexes, such as serum cholinesterase, albumin, and blood urea nitrogen to creatinine ratio, demonstrated either protective or risk factors for prognosis. Injury and comorbidities, including acute renal failure, chronic lung disease, and Glasgow Coma Scale, were identified as risk factors for mortality. Scoring tools like Acute Physiological and Chronic Health Evaluation (APACHE) II score, CURB-65 score, and Pneumonia Severity Index (PSI) score showed associations with mortality. Lastly, certain treatment protocols, such as vasoactive agent use, vasopressor use, and mechanical ventilation, were found to increase the risk of mortality, while invasive mechanical ventilation and the use of remdesivir and steroids had a positive impact on prognosis. These findings provide valuable insights for clinicians in predicting and managing severe pneumonia outcomes.

Conclusion • This most comprehensive review identified 53 unique prognostic factors of severe pneumonia, which provided a reference for subsequent researchers to construct models to predict clinical outcomes in patients with severe pneumonia for clinical use. By identifying prognostic factors through multivariate analysis, healthcare providers can better assess the severity and prognosis of individual patients. This knowledge can aid in treatment planning, resource allocation, and determining the appropriate level of care for patients with severe pneumonia. Additionally, understanding the prognostic factors can help identify high-risk patients who may require more intensive monitoring or interventions. Overall, this study provides valuable insights that can inform clinical practice and improve patient outcomes in the management of severe pneumonia. (*Altern Ther Health Med.* 2024;30(5):80-89)

Yanliang Yang, BM; Attending doctor; **Qianying Wang,** BM; Attending doctor; **Zhiwei Yu,** MM; Associate chief physician; Geriatrics department, Xinchang Hospital affiliated to Shaoxing University Medical College.

Corresponding author: Zhiwei Yu, MM
E-mail: yzwtxzz1983@163.com

INTRODUCTION

Severe pneumonia was defined as pneumonia presenting with severe hypoxemia or acute respiratory failure requiring ventilation support, or circulatory failure such as hypotension, shock, and other organ dysfunction.[1] Respiratory failure is a condition where the respiratory system fails to maintain adequate gas exchange, specifically oxygenation and carbon dioxide elimination. In severe pneumonia, respiratory failure is typically characterized by hypoxemia (insufficient blood oxygen levels) and/or hypercapnia (elevated blood carbon dioxide levels). This occurs due to inflammation and infection in the lungs, which impairs the normal function of the respiratory system. Circulatory failure refers to compromised blood flow and inadequate tissue perfusion due to impaired cardiac function. In severe pneumonia, circulatory failure can occur as a result of the infection and inflammation affecting the heart and blood vessels. Reduced cardiac output and altered vascular resistance contribute to inadequate blood circulation, leading to

compromised tissue perfusion throughout the body. The overall prevalence of severe pneumonia was 7.13 per 1000 person-years, in males 7.32 and females 6.93 per 1000 person-years, respectively, and varied markedly by region.[2] From a global perspective, pneumonia is a disease that needs to be solved and treated urgently, posing a great threat to human life and health safety. Certainly, the global perspective and the impact of the COVID-19 pandemic on severe pneumonia are significant. The COVID-19 pandemic has led to a substantial increase in severe pneumonia cases worldwide.[3] According to data from various sources, including the World Health Organization (WHO), as of the current date, there have been millions of confirmed cases of COVID-19 globally, with a significant proportion of these cases experiencing severe respiratory symptoms. For instance, studies have shown that a considerable number of COVID-19 patients develop severe pneumonia, requiring hospitalization and intensive care. The severity of pneumonia in COVID-19 can be attributed to the unique characteristics of the SARS-CoV-2 virus, which causes the disease. The virus has a high transmission rate and can lead to severe respiratory distress syndrome in certain individuals. This has resulted in an increased burden on healthcare systems worldwide, with hospitals and intensive care units being overwhelmed in some regions. Moreover, the impact of the COVID-19 pandemic on severe pneumonia extends beyond the direct effects of the virus. Indirectly, the pandemic has disrupted healthcare systems, limited access to medical care for non-COVID-19 conditions, and created challenges in managing severe pneumonia cases. These factors have further contributed to the complexity and severity of pneumonia cases during this global health crisis. It is important to note that specific statistics and data regarding the increase in severe pneumonia cases during the COVID-19 pandemic may vary across countries and regions. However, the overall trend indicates a significant rise in the number of severe pneumonia cases due to COVID-19, highlighting the urgent need for effective prevention, diagnosis, and management strategies.

Severe pneumonia was usually accompanied by a variety of underlying diseases,[4] such as dyspnea[5] and cardiovascular dysfunction.[6]In general, severe pneumonia can be triggered by various underlying conditions. Chronic obstructive pulmonary disease (COPD): This is a progressive lung disease that causes breathing difficulties and increases the risk of developing pneumonia. Asthma: People with asthma have inflamed airways, making them more vulnerable to respiratory infections like pneumonia. Immunodeficiency: Individuals with weakened immune systems, such as those with HIV/AIDS, certain cancers, or on immunosuppressive medications, are at a higher risk of developing severe pneumonia. Diabetes mellitus: Uncontrolled diabetes weakens the immune system, making individuals more susceptible to pneumonia and its complications. Heart disease: Conditions like congestive heart failure or coronary artery disease can impair lung function and increase the likelihood of severe pneumonia. Liver or kidney disease: Impaired liver or kidney function can affect the body's ability to fight off infections properly, including pneumonia. Older adults, particularly those over 65 years old, have a higher risk of developing severe pneumonia due to natural aging-related changes in the respiratory system and weakened immunity. Smoking damages the lungs and impairs the ciliary function responsible for clearing mucus and bacteria from the airways, increasing the susceptibility to pneumonia. Certain lifestyle habits, such as excessive alcohol consumption, poor nutrition, and lack of physical exercise, can also contribute to weakened immune function and increase the risk of severe pneumonia. When severe pneumonia develops, persistent harmful effects on the circulatory system are caused, mainly manifested as a weak pulse and rapid heart rate. Severe infections can even lead to septic shock. Since severe pneumonia progresses rapidly, it is difficult to treat and has a high mortality.[7] Active and rapid infection control can reduce the occurrence of complications, and effective prevention and treatment measures taken early can reduce the death rate of severe pneumonia. Therefore, it is significant to explore the risk factors that affect the prognosis of severe pneumonia.

At present, a large body of evidence has reported prognostic factors of severe pneumonia, including male sex and mechanical ventilation,[8] older age, and concomitant interstitial lung disease.[9] However, there has not been a systematic review to comprehensively elaborate the relevant influencing factors. Identifying risk factors for the prognosis of severe pneumonia is highly significant for several reasons. Firstly, it allows healthcare providers to accurately assess the severity and prognosis of individual patients. By understanding which factors are associated with worse outcomes, healthcare providers can identify high-risk patients who may require more intensive monitoring, aggressive treatment, or specialized care. This information helps in resource allocation, ensuring that appropriate interventions are provided to those who need them the most. Secondly, identifying prognostic factors helps in medical decision-making. Healthcare providers can use this information to make informed decisions regarding treatment options, such as the choice of antibiotics, the need for oxygen therapy, or the initiation of mechanical ventilation. It enables personalized medicine and tailored approaches to patient care. Furthermore, knowledge of prognostic factors can assist in patient counseling and communication. Healthcare providers can discuss the potential risks and outcomes with patients and their families, facilitating shared decision-making and setting realistic expectations. This information empowers patients to actively participate in their care and make informed choices about treatment options. From a public health perspective, identifying risk factors for severe pneumonia can inform preventive strategies. For instance, if certain demographic or clinical characteristics are found to be associated with worse outcomes, targeted interventions can be implemented to reduce the risk and severity of pneumonia in vulnerable populations. This may include vaccination campaigns, public health education, or lifestyle modifications. Overall, the identification of risk factors for the prognosis of severe pneumonia has practical implications for both healthcare providers and patients. It improves risk stratification, guides medical decision-making, facilitates patient counseling, and informs preventive strategies. Ultimately, this knowledge contributes to better patient

outcomes, more efficient allocation of resources, and improved management of severe pneumonia.

The existing literature on severe pneumonia prognosis has mainly focused on individual risk factors, such as age, comorbidities, and clinical presentation. However, there is a lack of comprehensive reviews that synthesize the available evidence on prognostic factors for severe pneumonia. A systematic review can help to address this gap by providing a comprehensive overview of the current evidence on prognostic factors for severe pneumonia. This study aims to fill this gap by conducting a systematic review of the literature on prognostic factors for severe pneumonia. By synthesizing the available evidence, this study aims to identify the most important prognostic factors associated with poor outcomes in severe pneumonia. This information can be used to develop predictive models that can aid in clinical decision-making and improve patient outcomes. Furthermore, this study will also explore the heterogeneity of the existing literature, including differences in study design, population characteristics, and outcome measures. This analysis will provide insights into the limitations of existing research and highlight areas for future research. In summary, this study aims to fill the research gap by conducting a comprehensive systematic review of the literature on prognostic factors for severe pneumonia. By synthesizing the available evidence, this study hopes to identify the most important prognostic factors associated with poor outcomes, which can inform clinical decision-making and improve patient outcomes.

METHODS

We extracted information from all eligible publications using standardized data extraction tables and reviewed adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.[10]

Literature search

Two investigators performed independent searches in Pubmed, Embase, and Web of Science from inception to March 2023 to find cohort studies investigating the association between prognostic factors and adverse outcomes of severe pneumonia in adult patients, without any limitation of publication date. Full search strategy was developed using Medical Subject Headings terms and recorded in Supplementary Table 1. Key search terms were related to severe pneumonia ("severe pneumonia" OR "severe pneumonitis" OR "severe pulmonary inflammation" OR "severe lung inflammation") and prognostic study (prognosis OR diagnosed OR cohort OR predictor OR death OR "models, statistical"). In order not to miss any appropriate study, the reference lists of review articles were checked manually for additional eligible studies. Any discrepancies were resolved by a third investigator for the final decision. Endnote X9 software was employed in article management and selection, and it help to eliminate the duplicates.

Study selection

The title and abstract of the article were initially screened so as to identify the relevant study. If any paper had an ambiguous abstract, or even a missed abstract, the full text would be obtained and screened. The following inclusion and exclusion criteria were used to determine which articles were eligible for the data extraction. Any disagreement over the eligibility of particular studies was resolved through discussion with a third reviewer.

Studies were included for the current research if satisfying all the following criteria: (1) related to severe pneumonia in adult patients, (2) the study had a prospective or retrospective longitudinal design, with at least one follow-up time point, (3) investigated prognostic factors, (4) performed multivariate analysis to assess significance of prognostic factors. Exclusion criteria were listed as follows: (1) not in English or Chinese, (2) only investigated severe pneumonia in children, (3) only conducted univariate analysis, (4) conference abstracts, reviews, and case reports.

Data extraction

Two investigators independently extracted the following data from eligible studies: the first author's name, country, year of publication, study design, sample characteristics, sample size, gender composition, average age, analysis method, significant prognostic factor, outcome, effect estimates and corresponding 95% confidence intervals (CI). In this study, effect estimates included hazard ratio and odds ratio (OR). For comparison, OR were uniformly utilized to represent the association between prognostic factors and adverse outcomes. When discrepancies in data extraction occurred between the two investigators, they were resolved through consensus with a third reviewer. The third reviewer, who was independent and impartial, carefully reviewed the conflicting data and discussed it with the two investigators. Through open and transparent discussions, the three reviewers worked together to reach a consensus on the accurate and reliable data to be extracted. The involvement of a third reviewer in resolving disagreements adds an additional layer of objectivity and reliability to the data extraction process. It helps ensure that the final data compiled into spreadsheets is accurate and consistent across the included studies. The resolution of discrepancies through consensus among multiple reviewers enhances the reliability and validity of the data extraction process in this study. All the data that was retrieved from the studies that qualified for the final inclusion was compiled into spreadsheets.

Quality assessment

The methodological quality of eligible studies was independently evaluated by the same researchers utilizing the Quality In Prognosis Studies (QUIPS) tool.[11] The QUIPS tool assesses the risk of bias in prognostic studies by appraising each article from six important domains: 1) study participation, 2) study attrition, 3) measurement of prognostic factors, 4) measurement of outcomes, 5) measurement of confounding, and 6) statistical analysis and reporting. The detailed evaluation criteria of each domain were documented in Hayden et al's article.[11] For each study, two independent

assessors judged the risk of bias for each of the six domains as low, moderate, or high. According to the recommendation by Sheehan et al.[12], studies were assigned an overall high risk of bias if one or more domains were considered high risk. Studies were assigned a moderate risk of bias if three or more domains were moderate risk and none were high risk. Studies were assigned a low risk of bias if three or more domains were low risk and none were high risk. A consensus meeting followed during which the two assessors reached an agreement upon judgments for each of the six domains and overall risk of bias for each study.

Data analysis

The prognostic factors evaluated in each study were classified as either significant or not significant. Significance was defined as having $P < .05$ and a 95% confidence interval. Prognostic factors' significance calculated with univariate analyses were disregarded. Among significant prognostic factors, those with OR < 1 were recognized as protective factors, and those with OR > 1 were considered as risk factors of prognosis. Furthermore, the association between the factor and prognosis was very weak while OR at 1.0-1.1 or 0.9-1.0, weak while OR at 1.2-1.4 or 0.7-0.8, moderate while OR at 1.5-2.9 or 0.4-0.6, strong while OR at 3.0-9.0 or 0.1-0.3, very strong while OR over 10 or less than 0.1.

RESULTS

Figure 1 depicts the flow diagram of the study selection process. The search strategy identified 1,916 articles with six articles identified from additional retrieval. After removing the duplicate records, the title and abstract of 1588 articles were screened for eligibility. As a result, 114 articles remained. After retrieving 114 full-text articles, 27 articles were considered eligible for this systematic review.

Study characteristics

Table 1 describes characteristics of the included prognostic studies on severe pneumonia. 27 published prognostic studies,[13-39] including 7 prospective cohort studies and 20 retrospective cohort studies, reported 71 OR values

Figure 1. The flow diagram of study selection.

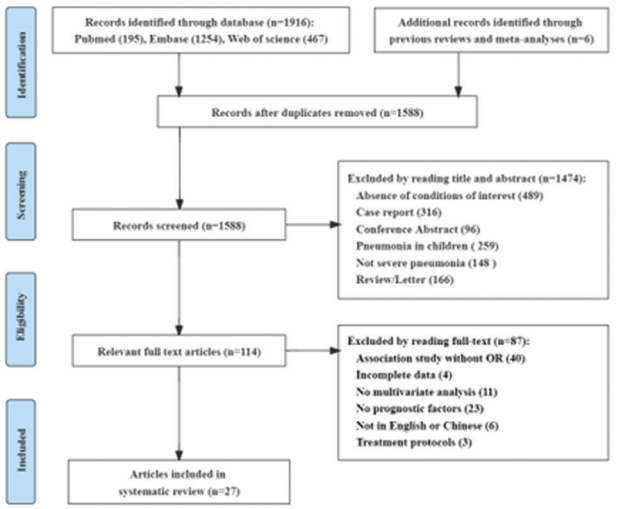
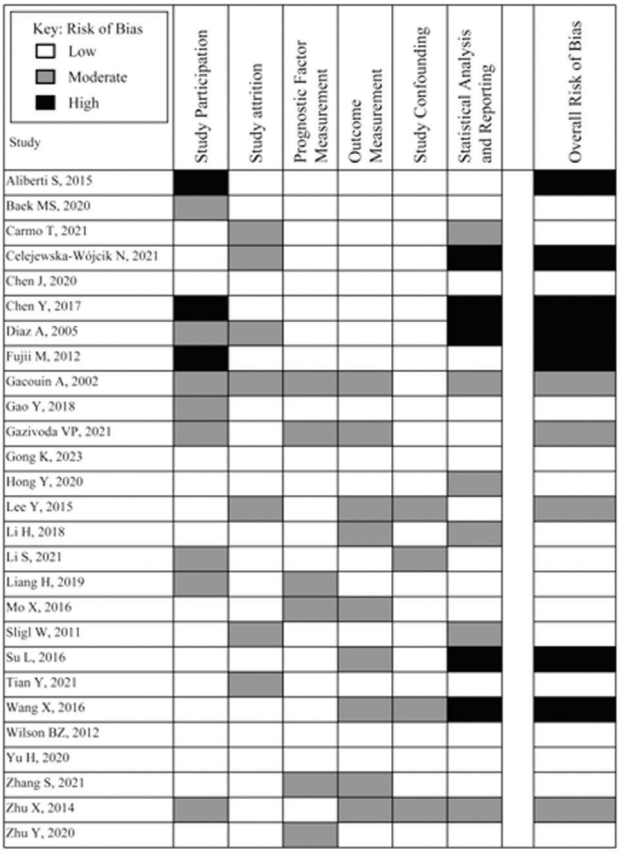


Table 1. Characteristics of the included prognostic studies on severe pneumonia.

Study	Country	Design	Sample characteristics	Sample size	Male (%)	Prognostic factor
Aliberti S, 2015	Italy	Retrospective	Patients with severe pneumonia	172	78.0	Delirium symptom, Charlson comorbidity index > 3, Severe sepsis
Baek MS, 2020	Korea	Retrospective	Severe pneumonia aged ≥ 80 years	412	50.0	Chronic lung disease, Mechanical ventilation, Hemodialysis, Albumin
Carmo T, 2021	Brazil	Prospective	Patients with severe pneumonia	200	48.0	Age ≥ 75 years, Sodium ≥ 145 mmol/L, Vasopressor use, Glasgow Coma Scale < 15
Celejewska-Wójcik N, 2021	Poland	Prospective	Acute respiratory failure in severe COVID 19 pneumonia	116	78.4	The ROX index < 3.85
Chen J, 2020	China	Retrospective	Patients with severe pneumonia	115	65.2	COPD, Vasopressor use, CRRT, APACHE II score, MPV
Chen Y, 2017	China	Retrospective	LOSP in patients who underwent allogeneic hematopoietic stem cell transplantation	68	69.1	PCT ≥ 0.94 μg/L
Diaz A, 2005	Spain	Prospective	Severe community-acquired pneumonia	113	58.4	Glucose >300 mg/dL, Acute renal failure
Fujii M, 2012	Japan	Retrospective	In elderly patients with severe pneumonia	71	64.8	Emphysematous changes on thoracic CT, Albumin < 3.0 g/dL
Gacouin A, 2002	France	Retrospective	Patients with severe Legionella pneumonia	43	83.7	SAPS II > 46, Symptoms duration >5 days
Gao Y, 2018	China	Retrospective	Severe pneumonia patients with ARDS complicated with septic shock	52	61.5	sFlt-1, EVLWI
Gazivoda VP, 2021	USA	Retrospective	Critically Ill COVID-19 Patients With Severe Pneumonia	281	68.3	Barotrauma, Age, Renal Dysfunction, Remdesivir, Steroids
Gong K, 2023	China	Retrospective	Elderly patients with severe CAP	130	50.0	Serum TUG1, CURB-65 score, PSI
Hong Y, 2020	China	Retrospective	Patients with critical pneumonia	126	54.8	GLI, CRP/albumin ratio, APACHE II score, CURB-65 score
Lee Y, 2015	Korea	Retrospective	Patients with severe pneumonia	152	75.0	APACHE II score, Troponin I
Li H, 2018	China	Retrospective	Severe community-acquired pneumonia	88	69.3	Heart rates, No invasive mechanical ventilation
Li S, 2021	China	Prospective	Severe pneumonia patients with Severe ARDS	65	63.1	sICAM-1, KL-6
Liang H, 2019	China	Retrospective	Patients with severe pneumonia	214	55.1	NLR, PCT, Lac, APACHE II score
Mo X, 2016	China	Retrospective	Patients with severe pneumonia	86	55.8	S-ChE, APACHE II score, MODS score
Sligl W, 2011	Canada	Prospective	Patients with severe pneumonia	271	59.0	Functionally completely dependent
Su L, 2016	China	Prospective	Severe healthcare-associated pneumonia	145	64.1	CURB-65 score 3-5
Tian Y, 2021	China	Retrospective	Patients with severe pneumonia	212	70.8	Vasopressor use, CRRT, UAR
Wang X, 2016	China	Retrospective	Elderly patients with severe pneumonia	272	63.2	Age ≥ 70 years,
Wilson BZ, 2012	USA	Retrospective	Elderly patients with severe pneumonia	1989	98.5	The use of beta-lactam + fluoroquinolone
Yu H, 2020	China	Retrospective	Patients with severe pneumonia	125	64.8	APACHE II score, Glucose, Fentanyl, RBC transfusion
Zhang S, 2021	China	Prospective	Patients with severe pneumonia	408	62.3	PSI >level 3, UCR >108.7
Zhu X, 2014	China	Retrospective	Elderly patients with severe pneumonia	81	60.5	Age ≥ 65 years
Zhu Y, 2020	China	Retrospective	Patients with severe pneumonia	89	58.4	Age, Ventilator dependency, Vasoactive agents, Blood urea nitrogen on admission, New hyperchloremia

Abbreviations: ROX, The ratio of oxygen saturation / fraction of inspired oxygen to respiratory rate; COPD, chronic obstructive pulmonary disease; CRRT, Continuous renal replacement therapy; APACHE II, Acute Physiological and Chronic Health Evaluation II score; MPV, Mean platelet volume; PCT, Procalcitonin; SAPS II, Simplified acute physiology score II; sFlt-1, Plasma soluble vascular endothelial growth factor receptor; EVLWI, Extravascular lung water index; PSI, Pneumonia Severity Index; GLI, Glycaemic lability index; CRP, C-reaction protein; sICAM-1, Soluble intercellular adhesion molecule-; KL-6, Krebs von den lungen-6; NLR, Neutrophil to lymphocyte ratio; Lac, Blood lactic acid; S-ChE, Serum cholinesterase; MODS score, Multiple organ dysfunction syndrome score; UAR, Urea-to-albumin ratio; RBC, Red blood cell; UCR, Blood urea nitrogen to creatinine ratio.

Figure 2. Risk of bias assessment using the Quality in Prognosis Studies (QUIPS) tool.



for 53 different prognostic factors and covered 4 unique outcomes. We classified 53 different prognostic factors into six categories, consisting of demographics (1 factor with 5 OR values), anthropometric indexes (3 factors with 4 OR values), laboratory indexes (22 factors with 24 OR values), injury and comorbidities (12 factors with 13 OR values), scoring tool (4 factors with 12 OR values), treatments (11 factors with 14 OR values). 4 unique outcomes included mortality at different follow-up time points, extubation failure, increased mean length of stay, and inability to be weaned from mechanical ventilation. All studies were published between 2002 and 2023 and totally included 6,096 patients. Sample size ranged from 43 to 1989 patients.

Table 2. Demographics prognostic factors of severe pneumonia on multivariate analysis.

Study	Prognostic factor	Outcome	OR (95% CI)	*P* value
Gazivoda VP, 2021	Age	30-day mortality	1.015 (1.004, 1.027)	.006
Zhu Y, 2020	Age	30-day mortality after entering ICU	1.060 (1.018, 1.104)	.005
Zhu X, 2014	Age ≥ 65 years	mortality	6.675 (2.620, 15.731)	.001
Wang X, 2016	Age ≥ 70 years	mortality	7.020 (3.270, 18.690)	.030
Carmo T, 2021	Age ≥ 75 years	Intensive care unit mortality	3.460 (1.510, 7.930)	.030

Table 3. Prognostic studies on severe pneumonia with anthropometric indexes.

Study	Prognostic factor	Outcome	OR (95% CI)	*P* value
Sligl W, 2011	Functionally completely dependent	30-day mortality	5.300 (2.000, 14.100)	<.001
Sligl W, 2011	Functionally completely dependent	1-year mortality	3.000 (1.500, 6.100)	.002
Li H, 2018	Heart rates	Mortality	1.081 (1.003, 1.165)	.042
Celejewska-Wójcik N, 2021	The ratio of oxygen saturation / fraction of inspired oxygen to respiratory rate index < 3.85	30-day mortality	6.100 (3.040, 12.260)	NP

Abbreviations: NP, not published.

Table 4. Prognostic studies on severe pneumonia with laboratory indexes.

Study	Prognostic factor	Outcome	OR (95% CI)	*P* value
Baek MS, 2020	Albumin	In-hospital mortality	0.431 (0.213, 0.873)	.019
Fujii M, 2012	Albumin < 3.0 g/dL	Weaning from mechanical ventilation	4.250 (1.170, 15.450)	.030
Liang H, 2019	Blood lactic acid	28-day mortality	1.263 (1.011, 1.579)	.040
Zhu Y, 2020	Blood urea nitrogen on admission	30-day mortality after entering ICU	1.168 (1.029, 1.325)	.016
Zhang S, 2021	Blood urea nitrogen to creatinine ratio > 108.7	Mortality	0.545 (0.332, 0.896)	.017
Hong Y, 2020	CRP/albumin ratio	28-day mortality	3.728 (1.213, 10.017)	<.001
Gao Y, 2018	Extravascular lung water index	28-day mortality	3.520 (2.850, 6.490)	.006
Yu H, 2020	Glucose	Extubation failure	1.122 (1.008, 1.249)	.035
Diaz A, 2005	Glucose > 300 mg/dL	30-day mortality	7.200 (1.200, 42.700)	NP
Hong Y, 2020	Glycaemic lability index	28-day mortality	9.364 (3.817, 13.860)	<.001
Li S, 2021	Krebs von den lungen-6	28-day mortality	1.007 (1.001, 1.014)	.034
Chen J, 2020	Mean platelet volume	In-hospital mortality	2.267 (1.166, 4.406)	.016
Liang H, 2019	Neutrophil to lymphocyte ratio	28-day mortality	1.163 (1.007, 1.343)	.040
Zhu Y, 2020	New hyperchloremia occurred within 24 h after admission to the ICU	30-day mortality after entering ICU	21.714 (1.059, 445.008)	.046
Gao Y, 2018	Plasma soluble vascular endothelial growth factor receptor	28-day mortality	5.170 (3.420, 8.370)	.001
Liang H, 2019	Procalcitonin	28-day mortality	1.210 (1.098, 1.333)	.001
Chen Y, 2017	Procalcitonin ≥ 0.94 μg/L	Early death	5.770 (1.660, 20.110)	.006
Yu H, 2020	Red blood cell transfusion	Extubation failure	2.774 (1.062, 7.252)	.037
Mo X, 2016	Serum cholinesterase	Mortality	0.084 (0.017, 0.424)	.003
Gong K, 2023	Serum TUG1	30-day mortality	0.265 (0.098, 0.714)	.009
Carmo T, 2021	Sodium ≥ 145 mmol/L	Intensive care unit mortality	2.920 (1.210, 7.050)	.020
Li S, 2021	Soluble intercellular adhesion molecule-1	28-day mortality	1.014 (1.006, 1.022)	.001
Lee Y, 2015	Troponin I	Mortality	1.398 (1.005, 1.945)	.047
Tian Y, 2021	Urea-to-albumin ratio	In-hospital mortality	2.234 (1.146, 4.356)	.018

Abbreviations: NP, not published.

Quality assessment

The risk of bias assessment of the 27 included studies according to the Quality in Prognosis Studies (QUIPS) tool was shown in Figure 2. In total, 16 studies (59.3%) were classified as low overall risk of bias,[14,15,17,22,24,25,27,31,33,35-37,39] 4 studies (14.8%) had moderate overall risk of bias,[21,23,26,38] and 7 studies (25.9%) were considered with high overall risk of bias.[13,16,18-20,32,34] The main reasons for high bias assignment were study participation and statistical analysis and reporting. For instance, no inclusion and exclusion criteria were described in the manuscript,[13,18,20] the statistical report was not standardized or even wrong,[16,18,19,32,34] A total of 7 studies were rated as having a moderate risk of bias in the study attrition domain because there were some patients lost to follow-up and no comparisons were made between those lost follow-up and those observed during the study.[15,16,19,21,26,31,33] Besides, 6 studies did not provided clear definition and detection method of prognostic factors,[21,23,29,30,37,39] and 9 studies did not describe definite follow-up time point in the papers.[21,23,26,27,30,32,34,37,38] In particular, 4 studies did not adjust for any potential confounders.[26,28,34,38] The assessment of study quality using the QUIPS tool plays a critical role in interpreting the results of the systematic review. It allows for a more nuanced understanding of the reliability and validity of the evidence, influencing the overall confidence and strength of the conclusions drawn from the review.

Table 5. Prognostic studies on severe pneumonia with injury and comorbidities.

Study	Prognostic factor	Outcome	OR (95% CI)	*P* value
Diaz A, 2005	Acute renal failure	30-day mortality	5.100 (1.300, 19.900)	NP
Aliberti S, 2015	At least one delirium symptom	1-year mortality	2.350 (1.130, 4.900)	.023
Gazivoda VP, 2021	Barotrauma	30-day mortality	1.417 (1.040, 1.931)	.027
Aliberti S, 2015	Charlson comorbidity index > 3	1-year mortality	2.090 (1.060, 4.100)	.034
Baek MS, 2020	Chronic lung disease	In-hospital mortality	3.787 (1.256, 11.418)	.018
Chen J, 2020	COPD	In-hospital mortality	1.937 (1.017, 3.688)	.044
Fujii M, 2012	Emphysematous changes on thoracic CT	Unable to be weaned from mechanical ventilation	4.920 (1.080, 22.460)	.040
Carmo T, 2021	Glasgow Coma Scale < 15	Intensive care unit mortality	3.050 (1.270, 7.280)	.010
Mo X, 2016	Multiple organ dysfunction syndrome score	Mortality	2.189 (1.262, 3.800)	.005
Gazivoda VP, 2021	Renal Dysfunction	30-day mortality	1.602 (1.055, 2.432)	.027
Aliberti S, 2015	Severe sepsis	1-year mortality	2.120 (1.080, 4.180)	.030
Gacouin A, 2002	Symptoms duration > 5 days	Mortality	7.400 (1.170, 47.600)	NP

Abbreviations: NP, not published.

Table 6. Prognostic studies on severe pneumonia with scoring tools.

Study	Prognostic factor	Outcome	OR (95% CI)	*P* value
Chen J, 2020	APACHE II score	In-hospital mortality	1.074 (1.025, 1.126)	.003
Hong Y, 2020	APACHE II score	28-day mortality	2.701 (1.124, 7.712)	.024
Lee Y, 2015	APACHE II score	Mortality	1.056 (1.012, 1.102)	.012
Liang H, 2019	APACHE II score	28-day mortality	1.103 (1.032, 1.179)	.004
Mo X, 2016	APACHE II score	Mortality	1.675 (1.098, 2.556)	.017
Yu H, 2020	APACHE II score	Extubation failure	1.141 (1.022, 1.273)	.019
Gong K, 2023	CURB-65 score	30-day mortality	4.411 (1.156, 16.837)	.030
Hong Y, 2020	CURB-65 score	28-day mortality	10.721 (4.554, 17.336)	<.001
Su L, 2016	CURB-65 score 3-5	Mortality	1.955 (1.330, 2.875)	NP
Gong K, 2023	Pneumonia Severity Index	30-day mortality	4.600 (1.307, 16.193)	.017
Zhang S, 2021	Pneumonia Severity Index > level 3	Mortality	4.297 (2.777, 6.651)	<.001
Gacouin A, 2002	Simplified acute physiology score > 46	Mortality	8.700 (1.150, 66.750)	.036

Abbreviations: NP, not published.

Prognostic factors Demographics

Five articles investigated the association between age and prognosis of severe pneumonia (Table 2). Very slight relationships were observed between age and 30-day mortality in severe pneumonia patients when considering age as a continuous variable, with OR of 1.015 (1.004, 1.027) and 1.060 (1.018, 1.104). Of note, strong associations were found while considering age as a categorical variable, and ORs ranged from 3.460 to 6.675 for different age cut-off values.

Anthropometric indexes

Table 3 presents the anthropometric prognostic factors of severe pneumonia. Patients who were functionally completely dependent had a higher risk of 30-day mortality (OR, 5.300; 95% CI, 2.000-14.100) and 1-year mortality (OR, 3.000; 95% CI, 1.500-6.100) than patients who were independent. Very weak relationship was observed between heart rates and mortality in severe pneumonia patients, with an OR of 1.081 (1.003, 1.165). The ratio of oxygen saturation/fraction of inspired oxygen to respiratory rate index below 3.85 measured within the first 12 hours of therapy was related to increased 30-day mortality (OR, 6.100; 95% CI, 3.040-12.260).

Laboratory indexes

The results of 17 prognostic studies on severe pneumonia with laboratory indexes are shown in Table 4. Among 22 factors, 4 factors were protective factors of prognosis. Most notable was serum cholinesterase, which was demonstrated as a very strong protective factor for mortality, with an OR of 0.084 (0.017, 0.424). Two studies focused on albumin, one indicated that albumin was a protective factor for mortality, with OR of 0.431 (0.213, 0.873), and another demonstrated that patients with albumin < 3.0 g/dL were more unable to be weaned from mechanical ventilation. Patients with blood urea nitrogen to creatinine ratio > 108.7 had a lower risk of mortality, with an OR of 0.545 (0.332, 0.896). Serum TUG1 was also uncovered to decrease the risk of mortality in severe pneumonia patients (OR, 0.265; 95% CI, 0.098-0.714).

The other 18 factors were risk factors of prognosis. Most notably, CRP/albumin ratio (3.728; 95% CI, 1.213-10.017), extravascular lung water index (3.520; 95% CI, 2.850-6.490), glucose > 300 mg/dL (7.200; 95% CI, 1.200-42.700), glycaemic lability index (9.364; 95% CI, 3.817-13.860), plasma soluble vascular endothelial growth factor receptor (5.170; 95% CI, 3.420-8.370), and procalcitonin ≥ 0.94 μg/L (5.770; 95% CI, 1.660-20.110) were strongly associated with higher risk of mortality. Surprisingly, new hyperchloremia occurred within 24 h after admission to the ICU extremely raised the mortality risk of severe pneumonia patients, with OR of 21.714 (1.059, 445.008), but with poor credibility due to the wide 95% CI. Higher values of mean platelet volume urea/albumin ratio, and sodium ≥ 145 mmol/L were moderately elevated mortality risks in severe pneumonia patients. The need for red blood cells was a moderate risk factor for extubation failure. Besides, higher levels of blood lactic acid, procalcitonin, and troponin I were found to increase the risk of mortality with weak associations.

Injury and comorbidities

Table 5 documented prognostic studies on severe pneumonia with injury and comorbidities. Notably, acute renal failure (5.100; 95% CI, 1.300-19.900), chronic lung disease (3.787; 95% CI, 1.256-11.418), Glasgow Coma Scale < 15 (3.050; 95% CI, 1.270-7.280), symptoms duration > 5 days (7.400; 95% CI, 1.170-47.600) were strongly associated with a higher risk of mortality. Patients who experienced emphysematous changes on thoracic CT were more unable to be weaned from mechanical ventilation, with an OR of 4.920 (1.080, 22.460). Moreover, at least one delirium symptom, Charlson comorbidity index > 3, chronic obstructive pulmonary disease (COPD), higher multiple organ dysfunction syndrome score, and severe sepsis moderately elevated the risk of mortality. Barotrauma weakly increased the risk of 30-day mortality.

Scoring tools

Table 6 listed prognostic studies on severe pneumonia with scoring tools. Five researchers consistently reported that the Acute Physiological and Chronic Health Evaluation (APACHE) II score was related to a higher risk of mortality, with ORs ranging from 1.074 to 2.701. Three of them

Table 7. Prognostic studies on severe pneumonia with treatment protocols.

Study	Prognostic factor	Outcome	OR (95% CI)	*P* value
Chen J, 2020	Continuous renal replacement therapy	In-hospital mortality	1.956 (1.004, 3.809)	.048
Tian Y, 2021	Continuous renal replacement therapy	In-hospital mortality	1.679 (1.020, 2.762)	.041
Yu H, 2020	Fentanyl	Extubation failure	3.010 (1.100, 8.237)	.032
Baek MS, 2020	Hemodialysis	In-hospital mortality	4.320 (1.185, 15.744)	.027
Baek MS, 2020	Mechanical ventilation	In-hospital mortality	4.510 (1.809, 11.246)	.001
Li H, 2018	No invasive mechanical ventilation	Mortality	0.033 (0.001, 0.764)	.033
Gazivoda VP, 2021	Remdesivir	30-day mortality	0.479 (0.321, 0.714)	<.001
Gazivoda VP, 2021	Steroids	30-day mortality	0.488 (0.370, 0.643)	<.001
Wilson BZ, 2012	The use of beta-lactam + fluoroquinolone	Increased mean length of stay	1.300 (1.270, 1.330)	<.001
Zhu Y, 2020	Vasoactive agents	30-day mortality after entering ICU	21.068 (4.654, 95.376)	<.001
Carmo T, 2021	Vasopressor use	Intensive care unit mortality	4.280 (1.480, 12.320)	.010
Chen J, 2020	Vasopressor use	In-hospital mortality	1.842 (1.005, 3.373)	.048
Tian Y, 2021	Vasopressor use	In-hospital mortality	1.888 (1.226, 2.907)	.004
Zhu Y, 2020	Ventilator dependency	30-day mortality after entering ICU	6.679 (1.218, 36.620)	.029

presented weak associations, and two showed moderate links. One study revealed a very weak relationship between APACHE II score and the increased risk of extubation failure. Three articles focused on CURB-65 score, one indicated a strong association between CURB-65 score and elevated risk of mortality (OR, 4.411; 95% CI, 1.156-16.837), and one showed very strong association, with OR of 10.721 (4.554, 17.336), another found that patients with CURB-65 score at 3-5 had higher risk of death (1.955; 95% CI, 1.330-2.875). Strong links were observed both in a study considering Pneumonia Severity Index (PSI) as a continuous variable and a study setting PSI as a categorical variable, with ORs of 4.600 (1.307, 16.193) and 4.297 (2.777, 6.651), respectively.

Treatment protocols

Prognostic studies on severe pneumonia with treatment protocols were recorded in Table 7. It is worth noting that the use of vasoactive agents extremely increased mortality risk, with OR of 21.068 (4.654, 95.376). Besides, three articles focused on vasopressor use, two of them showed a moderate relationship with mortality, and one presented a strong association, with an OR of 4.280 (1.480, 12.320). The use of fentanyl (3.010; 95% CI, 1.100-8.237), hemodialysis (4.320; 95% CI, 1.185-15.744), mechanical ventilation (4.510; 95% CI, 1.809-11.246)) and ventilator dependency (6.679; 95% CI, 1.218-36.620) were strongly enhanced the risk of mortality. Two studies revealed that continuous renal replacement therapy moderately increased risk of in-hospital mortality. Interestingly, no invasive mechanical ventilation could extremely reduce mortality risk, with an OR of 0.033 (0.001, 0.764). The use of remdesivir and steroids also had a favorable effect on prognosis.

DISCUSSION

To our knowledge, this is the first systematic review of prognostic factors specific to severe pneumonia in adult patients. We identified 27 articles covering 53 unique prognostic factors, which were classified into six categories: demographics, anthropometric indexes, laboratory indexes, injury and comorbidities, scoring tools, and treatments. Overall, 7 studies scored high for risk of bias, and 4 scored moderate, others had low risk of bias. This was mainly due to the lack of recruitment criteria for participants and non-standard statistical reporting.

It is very important to understand that the key feature of a prognostic study design is that it aims to estimate a future clinical outcome based on more than one characteristic.[40] Therefore, only studies that had defined study participants and performed multivariate analysis with more than one variable were included in this research. Studies that focused on the association between severe pneumonia and a single prognostic factor were excluded. This ensured that significant risk factors have independent prognostic effects, which can provide a basis for the development of preventive strategies.

Age

Severe pneumonia is the most common infectious disease in elderly patients. Due to the elderly patients with decreased immune function are prone to become the high risk of severe pneumonia group, thus seriously affecting the physical health of elderly patients. The risk of death in elderly patients with severe pneumonia was 5.675 times higher than in younger patients.[38] With aging populations in countries around the world and increasing hospital admissions for pneumonia, early identification and intervention are critical.

Functional status

Sligl W et al disclosed that premorbid functional status was an independent predictor of both short- and long-term mortality in patients with pneumonia who are critically ill.[31] In the clinical management of patients with critical pneumonia, clinicians can consider measuring the premorbid functional status of patients, so as to make more accurate predictions of survival and give care recommendations to the families of patients with severe functional limitations and poor prognosis.

Laboratory indexes

As an indicator of nutritional status, albumin was found to be a significant protective factor for mortality and weaning from mechanical ventilation in patients with severe pneumonia. A line of studies had explored the influence of albumin on the outcomes of pneumonia. Todorova et al. reported that increased total serum protein and albumin values were of great value in successful weaning from mechanical ventilation.[41] Ma et al indicated that albumin could predict the short-term and long-term outcomes of community-acquired pneumonia patients with diabetes.[42] Therefore, it is necessary to develop a

nutritional treatment for patients with severe pneumonia. Besides, a strong protective effect of serum cholinesterase on mortality in severe pneumonia patients was observed. That was consistent with the latest research, which reported that serum cholinesterase played an important role in the inflammatory response and was associated with prognosis in COVID-19 pneumonia.[43]

Higher value of CRP/albumin ratio, extravascular lung water index, glucose > 300 mg/dL, glycaemic lability index, plasma soluble vascular endothelial growth factor receptor, and procalcitonin ≥ 0.94 μg/L suggests enhanced risk of mortality. The comprehensive presentation of the influence of laboratory indicators on the prognosis of severe pneumonia might assist clinicians with decision-making to help guide management strategies to optimize patient outcomes.

Scoring tools

Currently, APACHE II score, CURB-65 score, and PSI have been widely used to predict disease severity and mortality in severe pneumonia. The higher the score, the more serious the disease and the higher the mortality. In the present study, CURB-65 score and PIS were found to have a stronger association with mortality of severe pneumonia than APACHE II score. This finding was in line with the emerging study which demonstrated that PSI and CURB-65 score were good predictors of mortality in patients with COVID-19 pneumonia.[44]

Treatments

Interestingly, mechanical ventilation enhanced death risk while no invasive mechanical ventilation was an extremely significant favorable factor for mortality. As a common clinical intervention in senile patients with severe pneumonia, no invasive mechanical ventilation helps patients to grab the treatment opportunity. Note, that it is vital to pay attention to care respiratory tract and prevent reinfection during this rescue intervention. Long-term mechanical ventilation might be accompanied by a variety of complications, e.g. barotrauma, which leads to an increased risk of respiratory failure and thus increases the risk of death.[23] Additionally, clinicians need to pay caution when using vasoactive agents for severe pneumonia patients. Several studies disclosed the unfavorable effect of vasoactive agents in severe pneumonia.[15,39] Some common prevention and treatment methods for severe pneumonia, such as vaccination, antibiotic treatment, and mechanical ventilation, these measures have been proven to be effective in reducing the death rate from severe pneumonia. Vaccination helps prevent infection by stimulating the immune system to produce antibodies against specific pathogens. Antibiotics are used to treat bacterial pneumonia, which is a common cause of severe pneumonia. Mechanical ventilation provides support for patients who are unable to breathe adequately on their own. These additional measures enhance the comprehensive approach to preventing and treating severe pneumonia.

Strengths and limitations

The strengths of this review are the standard and systematic methods, consisting of a comprehensive search strategy of three scientific literature databases with independent study selection and extraction by two investigators, and systematic rating of risk of bias using QUIPS. Several potential limitations could not be ignored. First, the majority of the included studies were conducted in China, involving 5196 of the 6096 (85.2%) patients in this review, which might cause selection bias and limit the external generalization of the study. Second, some of the studies we included had very small sample sizes, which made the 95% CI span very large. That is, some small studies may give the impression that specific factors are significantly associated with poor prognosis for severe pneumonia, but this may be actually due to limited sample size (false positives).

Future perspectives

With a variety of disclosed prognostic factors, further screening could be carried out to select the most significant indicators, then a model would be developed and validated to predict clinical outcomes in patients with severe pneumonia. Next, the performance of the new model built based on these prognostic factors needed to be compared with existing prediction models. We hope a prediction model with good performance could be established to help clinical decision-making and management. Specifically, we have suggested exploring new risk factors for severe pneumonia to better understand its pathogenesis and identify new targets for intervention. Additionally, we have highlighted the importance of evaluating the effects of different treatment methods, including both pharmacological and non-pharmacological interventions, to optimize patient outcomes.

Besides, future studies with adequate sample size and among divers races are warranted to confirm the association between reported prognostic factors and severe pneumonia. To overcome the high risk of bias, well-designed prospective prognostic studies are needed with detailed recruitment criteria, methods and measurement of the prognostic factor and outcome, and non-standard statistical reporting. Moreover, it would be interesting not only to focus on mortality but also on other clinical outcomes, e.g. extubation failure, and increased length of stay.

The identification of significant prognostic factors associated with poor outcomes in severe pneumonia has important clinical implications for patient risk assessment and treatment strategies. The findings of this systematic review can inform clinical decision-making, providing healthcare practitioners with practical recommendations to improve patient outcomes. Based on the synthesis of the available evidence, we identified several significant prognostic factors associated with poor outcomes in severe pneumonia, including age, comorbidities, severity of illness, and laboratory parameters such as CRP, procalcitonin, and lymphocyte count. These findings suggest that healthcare practitioners should consider these factors when assessing patient risk and developing treatment strategies. For example, older patients

and those with comorbidities may be at higher risk of poor outcomes and may require more aggressive treatment or closer monitoring. Healthcare practitioners should also consider the severity of illness and laboratory parameters when assessing patient risk, as these factors can provide valuable information about disease progression and response to treatment. In terms of treatment strategies, the identification of significant prognostic factors can help guide therapy decisions. For example, patients with severe pneumonia who have high CRP levels or low lymphocyte counts may benefit from more aggressive antibiotic therapy or immunomodulatory agents. Similarly, patients with comorbidities may require additional interventions to manage their underlying conditions and prevent complications.

Overall, the identification of significant prognostic factors in severe pneumonia has important clinical implications for patient risk assessment and treatment strategies. Healthcare practitioners should consider these factors when assessing patient risk and developing treatment plans, using a personalized approach to optimize patient outcomes.

CONCLUSION

This comprehensive review has identified 53 unique prognostic factors associated with severe pneumonia. However, it is important to note that further research with larger sample sizes is needed to validate the predictive effect of some of these factors, particularly those reported in smaller studies. In the future, there is potential to develop a prediction model for clinical outcomes in patients with severe pneumonia based on these identified factors. This model can be compared with existing prediction models, and the optimal one can be selected for implementation in clinical practice. By evaluating factors such as age, body measures, laboratory indicators, injury and comorbidities, scoring tools, and treatment methods, clinicians can assess the prognosis of patients and develop personalized treatment plans accordingly. Additionally, these prognostic factors can be utilized to build predictive models that enable clinicians to more accurately assess clinical outcomes in patients with severe pneumonia. By incorporating basic patient information, laboratory test results, and other relevant metrics, a model can be developed that incorporates multiple predictors. Through this model, doctors can identify high-risk patients at an early stage based on their characteristics and score values, allowing for timely implementation of appropriate treatment measures. It is important to emphasize the need for further research and validation of these prognostic factors to enhance their reliability and applicability in clinical settings. By continually refining and improving predictive models, healthcare practitioners can better predict patient outcomes and provide more effective and targeted care for individuals with severe pneumonia..

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

YY and ZY designed the study and performed the experiments, YY and QW collected the data, ZY and QW analyzed the data, YY and ZY prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This study did not receive any funding in any form.

ETHICAL COMPLIANCE

Not applicable.

REFERENCES

1. Quinton LJ, Walkey AJ, Mizgerd JP. Integrative Physiology of Pneumonia. *Physiol Rev*. 2018;98(3):1417-1464. doi:10.1152/physrev.00032.2017
2. Sun Y, Li H, Pei Z, et al. Incidence of community-acquired pneumonia in urban China: A national population-based study. *Vaccine*. 2020;38(52):8362-8370. doi:10.1016/j.vaccine.2020.11.004
3. Xiong J, Zeng S, Xu H, Cao Y; Aggravated Respiratory Failure From COVID-19 Infection: Patient Care Management From Nurses in the Intensive Care Unit. *Altern Ther Health M*. 2021;27(228-232.
4. Montani D, Savale L, Noel N, et al; COMEBAC Study Group. Post-acute COVID-19 syndrome. *Eur Respir Rev*. 2022;31(163):210185. doi:10.1183/16000617.0185-2021
5. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*. 2020;25:100463. doi:10.1016/j.eclinm.2020.100463
6. Debeaumont D, Boujibar F, Ferrand-Devouge E, et al. Cardiopulmonary Exercise Testing to Assess Persistent Symptoms at 6 Months in People With COVID-19 Who Survived Hospitalization: A Pilot Study. *Phys Ther*. 2021;101(6):pzab099. doi:10.1093/ptj/pzab099
7. Climente-Martí M, Ruiz-Millo O, López-Cruz I, et al; Doctor Peset COVID-19 Working Group. Impact of intermediate to high doses of methylprednisolone on mortality rate in patients with COVID-19 pneumonia-induced severe systemic inflammation. *Int J Clin Pract*. 2021;75(9):e14479. doi:10.1111/ijcp.14479
8. Yoon HY, Shim SS, Kim SJ, et al. Long-Term Mortality and Prognostic Factors in Aspiration Pneumonia. *J Am Med Dir Assoc*. 2019;20(9):1098-1104.e4. doi:10.1016/j.jamda.2019.03.029
9. Ishikawa Y, Nakano K, Tokutsu K, et al. Estimation of treatment and prognostic factors of pneumocystis pneumonia in patients with connective tissue diseases. *RMD Open*. 2021;7(1):e001508. doi:10.1136/rmdopen-2020-001508
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
11. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158(4):280-286. doi:10.7326/0003-4819-158-4-201302190-00009
12. Sheehan KJ, Williamson L, Alexander J, et al. Prognostic factors of functional outcome after hip fracture surgery: a systematic review. *Age Ageing*. 2018;47(5):661-670. doi:10.1093/ageing/afy057
13. Aliberti S, Bellelli G, Belotti M, et al. Delirium symptoms during hospitalization predict long-term mortality in patients with severe pneumonia. *Aging Clin Exp Res*. 2015;27(4):523-531. doi:10.1007/s40520-014-0297-9
14. Baek MS, Park S, Choi JH, Kim CH, Hyun IG. Mortality and Prognostic Prediction in Very Elderly Patients With Severe Pneumonia. *J Intensive Care Med*. 2020;35(12):1405-1410. doi:10.1177/0885066619826045
15. Carmo TA, Ferreira IB, Menezes RC, et al. Derivation and Validation of a Novel Severity Scoring System for Pneumonia at Intensive Care Unit Admission. *Clin Infect Dis*. 2021;72(6):942-949. doi:10.1093/cid/ciaa183
16. Celejewska-Wójcik N, Polok K, Górka K, et al. High-flow nasal oxygen therapy in the treatment of acute respiratory failure in severe COVID-19 pneumonia: a prospective observational study. *Pol Arch Intern Med*. 2021;131(7-8):658-665. doi:10.20452/pamw.16015
17. Chen J, Li Y, Zeng Y, Tian Y, Wen Y, Wang Z; High Mean Platelet Volume Associates with In-Hospital Mortality in Severe Pneumonia Patients. High Mean Platelet Volume Associates with In-Hospital Mortality in Severe Pneumonia Patients. *Mediators Inflamm*. 2020;2020:8720535. doi:10.1155/2020/8720535
18. Chen Y, Wang Y, Jiang ZH, et al. [Analysis of risk factors related to the prognosis in patients with late-onset severe pneumonia after allogeneic hematopoietic stem cell transplantation]. *Zhonghua Nei Ke Za Zhi*. 2017;56(11):804-809.
19. Díaz A, Alvarez M, Callejas C, Rosso R, Schnettler K, Saldías F. [Clinical picture and prognostic factors for severe community-acquired pneumonia in adults admitted to the intensive care unit]. *Arch Bronconeumol*. 2005;41(1):20-26. doi:10.1016/S1579-2129(06)60390-X
20. Fujii M, Iwakami S, Takagi H, et al. Factors influencing weaning from mechanical ventilation in elderly patients with severe pneumonia. *Geriatr Gerontol Int*. 2012;12(2):277-283. doi:10.1111/j.1447-0594.2011.00765.x
21. Gacouin A, Le Tulzo Y, Lavoue S, et al. Severe pneumonia due to Legionella pneumophila: prognostic factors, impact of delayed appropriate antimicrobial therapy. *Intensive Care Med*. 2002;28(6):686-691. doi:10.1007/s00134-002-1304-8
22. Gao Y, Zhang G, Li S, et al. The predictive value of sFlt-1 combined with extravascular lung water index in severe pneumonia patients with acute respiratory distress syndrome complicated with septic shock. *Zhonghua Jizhen Yixue Zazhi*. 2018;27(12):1381-1387.
23. Gazivoda VP, Ibrahim M, Kangas-Dick A, Sun A, Silver M, Wiesel O. Outcomes of Barotrauma in Critically Ill COVID-19 Patients With Severe Pneumonia. *J Intensive Care Med*. 2021;36(10):1176-1183. doi:10.1177/08850666211023360
24. Gong K, Xu J, Tang J. Diagnostic and Prognostic Value of Deregulated Circulating Long Non-coding RNA TUG1 in Elderly Patients with Severe Pneumonia. *Inflammation*. 2023;46(1):313-321. doi:10.1007/s10753-022-01735-9
25. Hong Y, Li Y, Xu Z. Predictive value of GLI and CRP/albumin in patients with critical pneumonia. *Acta Med Mediter*. 2020;36(3):1957-1961.
26. Lee YJ, Lee H, Park JS, et al. Cardiac troponin I as a prognostic factor in critically ill pneumonia patients in the absence of acute coronary syndrome. *J Crit Care*. 2015;30(2):390-394. doi:10.1016/j.jcrc.2014.12.001
27. Li H, Lin X, Lin D, et al. Prognosis analysis of severe community-acquired pneumonia. *Zhongguo Huxi Yu Weizhong Jianhu Zazhi*. 2018;17(5):450-455.
28. Li S, Gao Y, Zhou L, et al. The prognosis evaluation of sICAM-1,KL-6 combined with EVLWI in severe pneumonia patients with acute respiratory distress syndrome. *Zhonghua Jizhen Yixue Zazhi*. 2021;30(6):730-736.
29. Liang H, Gao Y, Miao C, Song Y, He F. [Predictive value of neutrophil to lymphocyte ratio on 28-day mortality of patients with severe pneumonia]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2019;31(7):827-831. doi:10.3760/cma.j.issn.2095-4352.2019.07.006

30. Mo X, Tang H, Zeng L, Lu H, Guo L, Ma Z. [The value of determination of serum cholinesterase levels in judgment of severity and prognosis in patients with severe pneumonia]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2016;28(1):38-43. doi:10.3760/cma.j.issn.2095-4352.2016.01.008
31. Sligl WI, Eurich DT, Marrie TJ, Majumdar SR. Only severely limited, premorbid functional status is associated with short- and long-term mortality in patients with pneumonia who are critically ill: a prospective observational study. *Chest*. 2011;139(1):88-94. doi:10.1378/chest.10-1054
32. Su L, Chen B, Zou S. Early prognostic factors of mortality in patients with severe healthcare-associated pneumonia in the intensive care unit. *Int J Clin Exp Med*. 2016;9(7):14596-14603.
33. Tian Y, Li Y, Jiang Z, Chen J. Urea-to-Albumin Ratio and In-Hospital Mortality in Severe Pneumonia Patients. *Can J Infect Dis Med Microbiol*. 2021;2021:5105870. doi:10.1155/2021/5105870
34. Wang X, Liu X, Liu F. A study on the pathogen distribution and risk factors for death in 272 cases of severe pneumonia. *Journal of Pathogen Biology*. 2016;11(9):841-844.
35. Wilson BZ, Anzueto A, Restrepo MI, Pugh MJ, Mortensen EM. Comparison of two guideline-concordant antimicrobial combinations in elderly patients hospitalized with severe community-acquired pneumonia. *Crit Care Med*. 2012;40(8):2310-2314. doi:10.1097/CCM.0b013e31825151a8
36. Yu H, Luo J, Ni Y, et al. Early prediction of extubation failure in patients with severe pneumonia: a retrospective cohort study. *Biosci Rep*. 2020;40(2):BSR20192435. doi:10.1042/BSR20192435
37. Zhang S, Li M, Wang Q, Han Y. Predictive value of blood urea nitrogen to creatinine ratio in the condition and prognosis of severe pneumonia patients. *Zhongguo Huxi Yu Weizhong Jianhu Zazhi*. 2021;20(6):408-415.
38. Zhu X, Wang X, Zhao H. Drug resistance of pathogens isolated from elderly patients with severe pneumonia and risk factors for death. *Zhongguo Yiyuan Ganranxue Zazhi*. 2014;24(17):4250-4252.
39. Zhu Y, Zhang Z, Deng Q, An D, Zhang J, Chen X. Negative fluid balance can reduce the 30-day mortality after entering ICU of severe pneumonia patients: a retrospective cohort study. *Zhonghua Jizhen Yixue Zazhi*. 2020;29(8):1053-1058.
40. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ*. 2009;338(feb23 1):b375. doi:10.1136/bmj.b375
41. Todorova L, Temelkov A. Weaning from long-term mechanical ventilation: a nonpulmonary weaning index. *J Clin Monit Comput*. 2004;18(4):275-281. doi:10.1007/s10877-005-2221-5
42. Ma CM, Wang N, Su QW, et al. Age, Pulse, Urea, and Albumin Score: A Tool for Predicting the Short-Term and Long-Term Outcomes of Community-Acquired Pneumonia Patients With Diabetes. *Front Endocrinol (Lausanne)*. 2022;13:882977. doi:10.3389/fendo.2022.882977
43. Nakajima K, Abe T, Saji R, et al. Serum cholinesterase associated with COVID-19 pneumonia severity and mortality. *J Infect*. 2021;82(2):282-327. doi:10.1016/j.jinf.2020.08.021
44. Bradley J, Sbaih N, Chandler TR, Furmanek S, Ramirez JA, Cavallazzi R. Pneumonia Severity Index and CURB-65 Score Are Good Predictors of Mortality in Hospitalized Patients With SARS-CoV-2 Community-Acquired Pneumonia. *Chest*. 2022;161(4):927-936. doi:10.1016/j.chest.2021.10.031

Supplemental Table 1. Detailed search strategy in four databases PubMed, Embase, and Web of Science

PubMed		
	#1	("prognosis"[MeSH Terms] OR "diagnosed"[Title/Abstract] OR "cohort*"[Title/Abstract] OR "cohort effect"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "predictor*"[Title/Abstract] OR "death"[Title/Abstract] OR "models, statistical"[MeSH Terms])
	#2	("severe pneumonia"[Title/Abstract] OR "severe pneumonitis"[Title/Abstract] OR "severe pulmonary inflammation"[Title/Abstract] OR "severe lung inflammation"[Title/Abstract])
	#3	#1 AND #2
Embase		
	#1	'prognosis'/exp OR diagnosed OR cohort OR 'models, statistical'/exp OR 'models, statistical'
	#2	'severe pneumonia'/exp OR 'severe pneumonia' OR 'severe pneumonitis' OR 'severe pulmonary inflammation' OR 'severe lung inflammation'
	#3	#1 AND #2
Web of science		
	#1	(TS=(prognosis OR cohort OR "models, statistical")) OR AB=(diagnosed OR predictor OR death)
	#2	TS=("Severe Pneumonia" OR "Severe Pneumonitis" OR "Severe Pulmonary Inflammation" OR "Severe Lung Inflammation")
	#4	#1 AND #2