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ORIGINAL RESEARCH

Hyaluronic Acid is Associated with Severity and Prognosis in Patients with Community-Acquired Pneumonia

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Purpose: Hyaluronic acid (HA) is a novel inflammatory biomarker with a prognostic value for several infectious diseases. This study investigated the association of HA with severity and prognosis in hospitalized patients with community-acquired pneumonia (CAP).

Patients and Methods: We analyzed the differences of HA levels in different groups. Logistic regression analysis was performed to identify independent risk factors for severe CAP (SCAP). The predictive value of HA for SCAP was assessed using receiver operating characteristic (ROC) curves. Kaplan-Meier survival analysis was used to compare 30-day mortality between the high and low HA groups.

Results: Compared to healthy controls (49.2 ± 15.3 ng/mL), patients with CAP exhibited significantly elevated levels of HA ($P < 0.001$). In CAP patients, increased HA levels were more pronounced in those with SCAP (SCAP vs non-SCAP:135.6 ± 51 ng/mL vs 100.7 ± 47.8 ng/mL, $P < 0.001$). Compared to survivors (109.9 ± 48.7 ng/mL), HA levels in non-survivors were significantly higher (180.9 ± 67.8 ng/mL) ($P < 0.001$). HA was an independent predictor of SCAP [odds ratio (OR): 1.013, 95% confidence interval (CI): 1.003–1.022, $P = 0.011$] with high diagnostic accuracy [areas under the curve (AUC): 0.709, 95% CI: 0.622–0.797, $P = 0.001$]. Additionally, HA was independently associated with death risk in patients with CAP (OR: 1.022, 95% CI: 1.005–1.039, $P = 0.010$). Kaplan-Meier survival curves indicated that CAP patients in the high HA group exhibit a higher 30-day mortality rate compared to those in the low HA group (8.6% vs 1.5%, $P = 0.008$). Post hoc analysis indicated that our study possessed 98.857% statistical power.

Conclusion: In conclusion, High HA levels are associated with severity and mortality in patients with CAP, and HA could serve as a novel serum biomarker to predict the risk of CAP progression.

Keywords: hyaluronic acid, community-acquired pneumonia, severity, prognosis, biomarker

Introduction

Community-acquired pneumonia (CAP) is an acute respiratory disease that predominantly occurs outside healthcare facilities and is typically caused by one or more pathogens.[1] Despite advances in medical diagnosis and treatment strategies for CAP, it remains a threat to public health.[2] Severe CAP (SCAP) can lead to a range of serious complications, such as sepsis, septic shock, and even death.[3] During influenza epidemics, SCAP emerges as a major cause of mortality from infectious diseases.[4,5] The estimated mortality for hospitalized patients with SCAP ranges from 21% to 58%.[6] Therefore, early identification and management of high-risk CAP patients are crucial for improving clinical outcomes.

The severity of CAP is commonly stratified based on the risk assessment scale.[7] However, the clinical use of prognostic scoring systems such as the pneumonia severity index (PSI) and CURB-65 may be limited by suboptimal sensitivity and complex scoring procedures.[8,9] In recent years, serum inflammatory markers, such as C-X-C motif chemokine 10 (CXCL10),[10] interleukin-17 (IL-17),[11] and interleukin-23 (IL-23)[12] have emerged as non-invasive alternatives in predicting CAP severity and prognosis. Nevertheless, these biomarkers are pathogen-dependent, and assay

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sensitivity and cost may further limit their clinical use. Therefore, there is an urgent need to identify a broad-spectrum and cost-effective biomarker for early and accurate prediction of severe pulmonary infection.

Hyaluronic acid (HA), an integral component of the extracellular matrix (ECM),[13,14] is involved in multiple pathophysiological processes, including modulation of inflammation,[15,16] immune responses,[17,18] and microbial metabolism.[19,20] Clinical studies have demonstrated correlations between HA levels and various infectious diseases. A study by Schmidt et al[21] showed that serum HA levels were higher in patients with sepsis, and HA was positively correlated with the risk of death. Additionally, HA was found to be associated with a variety of lung conditions such as chronic obstructive pulmonary disease (COPD)[22] and respiratory distress syndrome (ARDS).[23] The production of HA is responsive to lung injury and plays a role in the regulation of various cellular behaviors.[24] HA stimulates macrophages to produce chemokines, which in turn facilitate the recruitment of neutrophils to sites of inflammation.[25] Furthermore, HA enhances the invasiveness of fibroblasts into the ECM and promotes the aggregation of myofibroblasts with collagen deposition, contributing to fibrosis and irreversible lung injury.[26] As a significant regulator of inflammatory responses and tissue repair,[27] HA is intimately linked to the progression of lung infections.[28]

Recent studies showed that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can enhance the accumulation of HA by activating the expression of hyaluronan synthase, a process that is significantly associated with the progression of lung infection.[29,30] However, it remains unclear whether HA correlates with the adverse outcomes in CAP. This study aims to assess the predictive value of HA for severity and mortality in hospitalized patients with CAP, thereby assisting clinicians in the early identification of individuals at high risk of disease progression.

Materials and Methods

Participating Patients and Controls

This study assessed the clinical characteristics of CAP patients admitted to Beijing Ditan Hospital between October 2023 and December 2023. A control group comprised individuals undergoing routine health check-ups at the same hospital. The median age of the healthy control group was 78 (66–84) years and there were 14 (46.7%) males. These demographic characteristics are aligned with the CAP group for a valid comparison. The ethics committee of Beijing Ditan Hospital approved the study. The data from patients were collected anonymously. The final cohort comprised 135 CAP patients and 30 healthy controls, with similar age and sex distribution.

Definition of CAP and SCAP

All patients in this study were adults aged 18 years or older diagnosed with CAP, defined by the following criteria:[31,32] (1) symptom onset in the community setting; (2) chest radiographs demonstrating new patchy infiltrates, lobar or segmental consolidation, ground-glass opacities, or interstitial changes; and (3) at least one clinical sign, including (a) cough, sputum production, or dyspnea; (b) a core body temperature of > 38.0°C; (c) abnormal breath sounds or increased respiratory rate; or (d) a peripheral white blood cell (WBC) count of $> 10 \times 10^9$/L or $< 4 \times 10^9$/L.

Recognizing the critical role of chest CT in the early assessment of pneumonia severity,[33,34] we incorporated specific imaging indicators into the diagnostic criteria for SCAP. In this study, SCAP was defined by the presence of at least one major criterion or three minor criteria: major criteria: (1) requirement for invasive mechanical ventilation; (2) occurrence of infectious shock necessitating vasopressor support. Minor criteria: (1) respiratory rate ≥ 30 breaths/min; (2) oxygenation index (PaO^2/FiO^2) ≤ 250; (3) multi-lobar infiltration; (4) confusion; (5) serum urea nitrogen ≥ 20 mg/dL; (6) WBC count ≤ 4×10^9/L; (7) platelet count < 100×10^9/L; (8) core body temperature < 36.0°C; (9) hypotension requiring aggressive fluid resuscitation; and (10) pulmonary consolidation accompanied by pleural effusion or ground-glass opacities.[35–37]

The exclusion criteria for this study were as follows: (1) age < 18 years; (2) pregnancy; (3) chronic liver diseases, such as liver fibrosis and cirrhosis; (4) severe underlying lung diseases, such as pulmonary fibrosis, pulmonary tuberculosis, and lung cancer; (5) acquired immunodeficiency syndrome; (6) administration of medications that influence HA metabolism, such as hymecromone.

Data Collection

The medical records included the following variables: demographic variables (such as age and sex), comorbidities (such as hypertension and diabetes mellitus), laboratory index [such as WBC and C-reactive protein (CRP)], chest imaging characteristics (such as bilateral lung infiltrates and pleural effusion), pathogens (bacteria, virus, and mixed), clinical severity scores (CURB-65 and PSI scores), and hospitalization (such as ICU admission and length of stay).

Measurement of HA Levels

Peripheral venous blood samples were collected upon admission. Serum samples were centrifuged for 15 min at 1200 × g and then stored at −20 °C until testing. The HA assay kits were purchased from the Nanjing Jiancheng Bioengineering Institute (H141-1-2). Serum HA concentrations were measured by a biochemical detector (Hitachi 7020, Japan), and we have taken two measurements for each sample, using the average of these values for our subsequent analysis. Serum HA concentrations were measured by a biochemical detector (Hitachi 7020, Japan), and we have taken two measurements for each sample, using the average of these values for our subsequent analysis.

Clinical Severity Scores Calculation

The CURB-65 score and PSI score are both important tools for assessing the severity of CAP.[38] The CURB-65 score consists of 5 dimensions, namely confusion, uremia, respiratory frequency, blood pressure, and age (Supplementary Table 1).[39] The PSI score consists of 3 demographic characteristics, 5 chronic complications, 5 physical findings, 6 laboratory measurements, and 1 imaging finding (Supplementary Table 2).[40]

Study Aims

In this study, the primary outcome was the diagnostic utility of HA for stratifying the severity of CAP, while the secondary outcome was the predictive value of HA levels concerning mortality in CAP patients.

Statistical Analysis

Continuous variables that followed normal distribution were presented as mean ± standard deviation, whereas those that followed abnormal distribution were expressed as median (interquartile range). Student's *t*-test or Mann–Whitney *U*-tests were used to compare the two groups. Categorical variables were presented as numbers (percentage) and were analyzed using chi-square tests, Fisher's exact test, or continuity chi-square corrections. Logistic regression analysis was applied to identify independent risk factors for SCAP and mortality. The Spearman correlation test was used to evaluate the correlations between variables with predictive value for CAP severity. The study utilized the receiver operating characteristic (ROC) curve to evaluate the discriminatory power of the diagnostic test in distinguishing between Non-SCAP and SCAP patients. Furthermore, ROC curve analysis was employed to ascertain the optimal diagnostic cutoff for predicting SCAP. The Youden index was utilized to identify the optimal cutoff point, calculated as follows:

Youden index = Sensitivity + Specificity – 1.

The optimal diagnostic threshold is the value corresponding to the maximum Youden index. The Kaplan-Meier method was used to compare the 30-day survival rates of CAP patients in different HA groups. Power Analysis and Sample Size (PASS) software was used to calculate statistical power. SPSS (version 26.0), GraphPad Prism (version 9.0), and R Studio (version 4.2.3) were used for statistical analysis. A two-sided P-value < 0.05 was considered statistically significant.

Results

Characteristics of the Enrolled Patients

In this study, 135 patients with CAP were categorized into two groups: non-SCAP (n = 85) and SCAP (n = 50). As shown in Table 1, the demographic and clinical characteristics of the non-SCAP and SCAP groups were similar, with no significant differences observed in body mass index (BMI), smoking status, comorbidities, or causative pathogens. Laboratory findings revealed that SCAP patients exhibited significantly elevated levels of aspartate aminotransferase,

Table 1 Baseline Characteristics of the Subjects Enrolled in This Study

Characteristics	All Patients (n=135)	Non-SCAP group (n=85)	SCAP Group (n=50)	P-value
Demographic variables				
Age (years)	69.0 (48.0–78.0)	64.0 (40.5–74.5)	71.0 (58.8–83.0)	**0.009**
Male, n (%)	79 (58.5%)	44 (51.8%)	35 (70.0%)	**0.038**
BMI (kg/m^2)	23.5 ± 3.7	23.6 ± 3.9	23.3 ± 3.4	0.609
Smoking, n (%)	42 (31.1%)	27 (31.8%)	15 (30.0%)	0.831
Comorbidities, n (%)				
Hypertension	51 (37.8%)	27 (31.8%)	24 (48.0%)	0.060
Diabetes mellitus	35 (25.9%)	20 (23.5%)	15 (30.0%)	0.407
Cardiovascular disease	35 (25.9%)	19 (22.4%)	16 (32.0%)	0.217
Cerebrovascular disease	17 (12.6%)	10 (11.8%)	7 (14.0%)	0.705
Liver disease	29 (21.5%)	17 (20.0%)	12 (24.0%)	0.585
Renal disease	15 (11.1%)	7 (8.2%)	8 (16.0%)	0.166
Malignancy	6 (4.4%)	5 (5.9%)	1 (2.0%)	0.532
Laboratory index				
Alanine aminotransferase (U/L)	18.0 (13.4–28.0)	18.0 (12.6–28.0)	20.0 (15.8–44.0)	0.068
Aspartate aminotransferase (U/L)	22.0 (16.0–31.0)	20.0 (15.7–27.5)	28.0 (16.2–48.8)	**0.007**
Total bilirubin (mg/dl)	10.0 (7.4–13.0)	9.0 (7.1–12.0)	10.0 (8.0–13.0)	0.070
Albumin (g/L)	37.3 ± 6.4	38.8 ± 6.6	34.8 ± 5.4	**0.001**
WBC (×10^9/L)	7.6 (5.3–10.9)	6.7 (5.0–10.0)	8.5 (6.2–12.7)	**0.003**
Lymphocytes (×10^9/L)	1.0 (0.7–1.6)	1.1 (0.7–1.7)	1.0 (0.7–1.4)	0.268
Neutrophils (×10^9/L)	5.6 (3.9–8.0)	5.1 (3.6–6.9)	7.0 (4.7–10.9)	**0.001**
NLR	5.2 (2.8–9.2)	4.5 (2.6–6.3)	8.5 (4.0–14.3)	**0.001**
Hemoglobin (g/dL)	129.0 (109.0–140.0)	130.0 (108.0–140.0)	125.5 (110.5–138.8)	0.469
Platelets (×10^9 /L)	196.0 (146.0–265.0)	209.0 (155.5–284.5)	182.5 (135.8–242.3)	0.058
eGFR (mL/min/1.73m^2)	94.0 ± 24.0	96.1 ± 22.8	90.6 ± 25.8	0.200
Glucose (mmol/L)	6.9 (5.6–9.5)	6.4 (5.5–9.0)	8.0 (5.8–10.4)	0.125
D-dimer (mg/L)	0.7 (0.4–1.4)	0.6 (0.3–0.9)	1.1 (0.6–1.7)	**<0.001**
Prothrombin time (s)	12.0 (11.0–13.5)	12.0 (11.0–13.0)	13.0 (11.0–14.0)	0.189
Fibrinogen (mg/dL)	439.0 (336.0–502.0)	390.0 (331.5–487.5)	469.0 (364.5–566.5)	**0.019**
CRP (mg/L)	47.0 (10.0–104.0)	33.0 (7.7–69.9)	72.0 (34.8–167.0)	**<0.001**
Procalcitonin (μg/L)	0.1 (0.0–0.4)	0.0 (0.0–0.1)	0.4 (0.1–1.0)	**<0.001**
HA (ng/mL)	105.0 (74.0–140.5)	88.0 (64.4–127.0)	129.9 (100.1–168.5)	**<0.001**
Chest X-ray, n (%)				
Bilateral lung infiltrates	113 (83.7%)	64 (75.3%)	49 (98.0%)	**0.001**
Pleural effusion	21 (15.6%)	2 (2.4%)	19 (38.0%)	**<0.001**
Pulmonary consolidation	44 (32.6%)	0 (0%)	44 (88.0%)	**<0.001**
Ground-glass opacity	66 (48.9%)	19 (22.4%)	47 (94.0%)	**<0.001**
Pathogens, n (%)				
Bacteria	47 (34.8%)	28 (32.9%)	19 (38.0%)	0.551
Virus	47 (34.8%)	32 (37.6%)	15 (30.0%)	0.368
Mixed	41 (30.4%)	25 (29.4%)	16 (32.0%)	0.752
Clinical severity scores				
CURB-6 score ≥ 3	16 (11.9%)	6 (7.1%)	10 (20.0%)	**0.048**
PSI ≥ IV	54 (40.0%)	24 (28.2%)	30 (60.0%)	**<0.001**

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients (n=135)	Non-SCAP group (n=85)	SCAP Group (n=50)	P-value
Hospitalization				
ICU admission	21 (15.6%)	4 (4.7%)	17 (34.0%)	**<0.001**
Length of stay (days)	12.0 (7.0–21.0)	9.0 (5.0–13.0)	21.5 (12.0–35.0)	**<0.001**
30-day mortality, n (%)	7 (5.2%)	1 (1.2%)	6 (12.0%)	**0.019**
Total mortality, n (%)	11 (8.1%)	2 (2.4%)	9 (18.0%)	**0.004**

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Bold text indicates P-value < 0.05.

Abbreviations: CAP, community-acquired pneumonia; SCAP, severe CAP; BMI, body mass index; WBC, white blood cells; NLR, neutrophil/lymphocyte ratio; eGFR, Estimated glomerular filtration rate; CRP, C-reactive protein; HA, hyaluronic acid; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥65 years old; PSI, pneumonia severity index; ICU, intensive care unit.

WBC, neutrophils, neutrophil/lymphocyte ratio (NLR), d-dimer, fibrinogen, CRP, and procalcitonin compared to non-SCAP patients ($p < 0.05$). Conversely, albumin levels were significantly lower in the SCAP group ($p = 0.001$). Chest radiographs indicated a higher prevalence of bilateral lung infiltrates (98.0%), pleural effusion (38.0%), solid lung lesions (88.0%), and ground-glass opacities (94.0%) in SCAP patients, which were significantly higher than the corresponding rates in non-SCAP patients (75.3%, 2.4%, 0.0%, and 22.4%, respectively; all $p < 0.05$). Severity scores classified a higher proportion of SCAP patients as high or intermediate-high risk compared to non-SCAP patients ($p < 0.05$). Additionally, 34.0% of SCAP patients required ICU admission, with a significantly longer hospital stay than non-SCAP patients. The 30-day and overall mortality rates were substantially higher in the SCAP group (12.0% and 18.0%) than in the non-SCAP group (1.2% and 2.4%, respectively; $p < 0.05$).

Serum HA Levels in Subgroups

As shown in Figure 1A, the serum HA levels in the SCAP group were significantly elevated at 135.6 ± 51 ng/mL compared to the non-SCAP group (100.7 ± 47.8 ng/mL) and the healthy control group (49.2 ± 15.3 ng/mL) ($P < 0.001$ for all group comparisons). Among CAP patients with different pathogens, including bacterial, viral, and mixed infections, no significant differences in HA levels were observed ($P > 0.05$) (Figure 1B). However, an association between disease severity and HA levels was noted, with higher HA levels correlating with increased severity. Specifically, HA levels were significantly lower in patients with low CURB-65 scores (<3) compared to those with high CURB-65 scores (≥3) ($P < 0.05$) (Figure 1C). Similarly, patients classified as intermediate to high-risk (≥ IV) by the PSI exhibited significantly higher HA levels than those in the low-risk group (< IV) ($P < 0.001$) (Figure 1D). Moreover, HA levels were markedly higher in the non-survivors (180.9 ± 67.8 ng/mL) than in the survivors (109.9 ± 48.7 ng/mL) ($P < 0.001$) (Figure 1E).

To elucidate the potential impact of comorbidities on HA levels in our study, we stratified CAP patients according to the presence of comorbidities and compared HA levels between subgroups with and without these conditions. Our analysis did not reveal any statistically significant differences in HA levels across the comorbidity subgroups (Supplementary Table 3). Therefore, there is no significant association between HA levels and any specific comorbidities in our research.

Association Between HA Levels and CAP Severity

To identify the determinants of severity in CAP patients, we performed a logistic regression analysis (Table 2). Variables with $P < 0.10$ in the univariate logistic regression analysis were included in the multivariate analysis. WBC [odds ratio (OR): 1.138, 95% confidence interval (CI): 1.019–1.271, $P = 0.022$], CURB-65 score (OR: 2.291, 95% CI: 1.271–4.313, $P = 0.010$), and HA (OR: 1.013, 95% CI: 1.003–1.022, $P = 0.011$) were identified as independent risk factors for the development of SCAP.

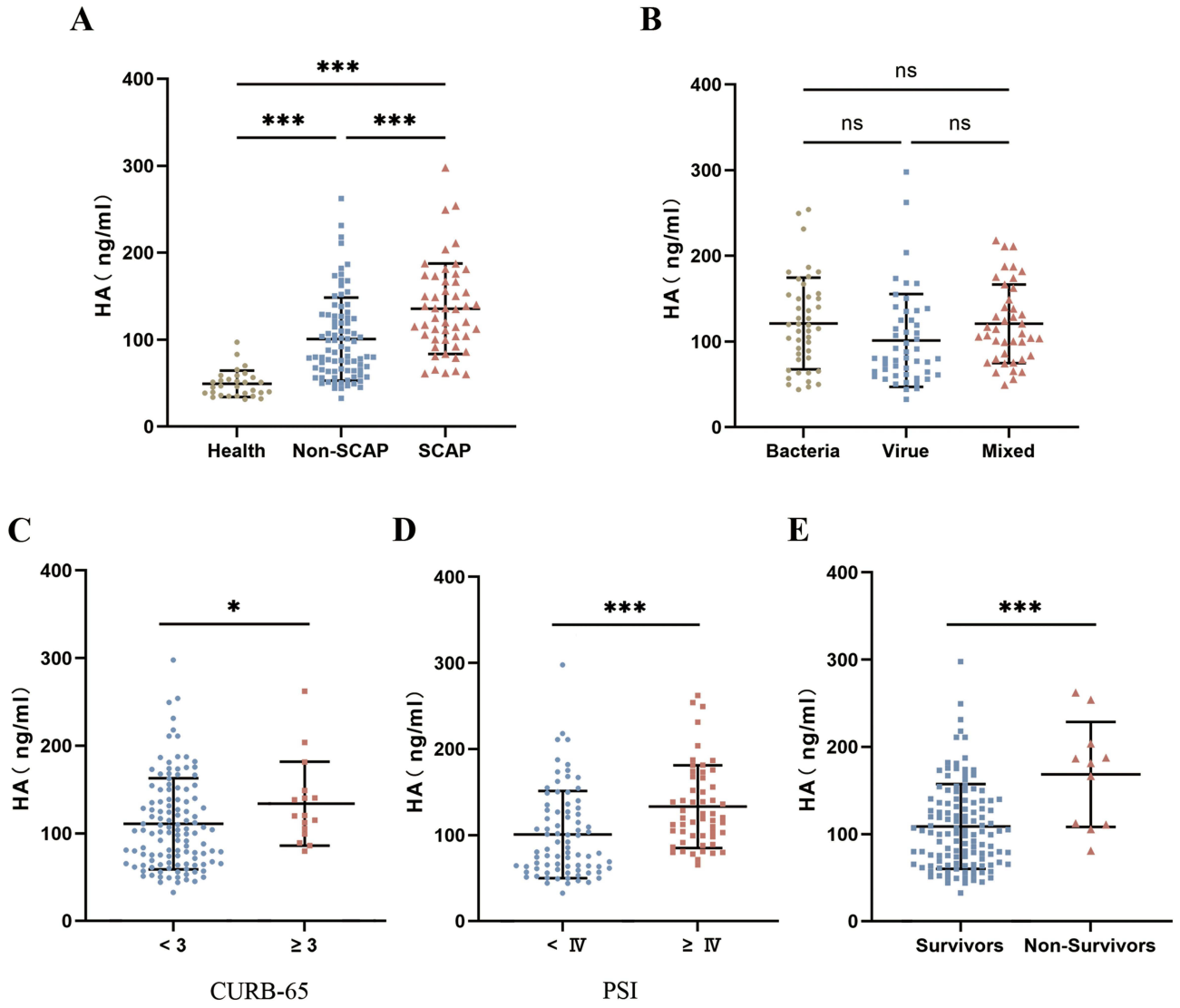

Figure 1 Levels of HA in patients with CAP across multiple groups. (**A**) Levels of HA in healthy controls, patients with non-SCAP, and patients with SCAP. (**B**) Comparison of HA in patients with CAP for various causative pathogens. (**C**) Levels of HA in different ranks of CURB-65 score of CAP patients. (**D**) Levels of HA in different ranks of PSI score of CAP patients. (**E**) Levels of HA in alive and dead CAP patients.

Notes: ns means not significant with P > 0.05, *P < 0.05, ***P < 0.001.

Abbreviations: HA, hyaluronic acid; CAP, community-acquired pneumonia; SCAP, severe CAP; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years old; PSI, pneumonia severity index.

Associations Between Predictors Levels

Spearman correlation analysis was conducted to explore the relationships between serum HA levels and various clinical parameters. The correlation matrix revealed significant positive associations between HA levels and the following clinical parameters: CURB-65, PSI, WBC, CRP, and NLR (P < 0.05) (Figure 2).

Predictive Capacities of HA in Predicting Severity in CAP Patients

Based on the results of the multivariate logistic regression analysis, WBC, HA, and the CURB-65 score were independent predictors of SCAP. The predictive performance of the three indicators for SCAP was assessed using the areas under the curve (AUC). For HA, the ROC curve analysis revealed an AUC of 0.709 (P = 0.001), indicating a significant diagnostic value for SCAP. The optimal cutoff value for HA to diagnose SCAP was determined to be 103.7 ng/mL, with a sensitivity of 74.0% and a specificity of 61.2%. The AUC for CURB-65 was 0.719 (95% CI: 0.635–0.804, P < 0.001), which was higher than that for HA, while the AUC for WBC was lower at 0.655 (95% CI: 0.228–0.753, P =

Table 2 Logistic Regression Analysis of Risk Factors Associated with SCAP

	Univariate Analysis		Multivariate Analysis	
	Odd ratio (95% CI)	**P-value**	**Odd ratio (95% CI)**	**P-value**
Age	1.024 (1.005–1.044)	0.014	0.997 (0.964–1.031)	0.858
Male	1.398 (0.689–2.837)	0.354		
BMI	0.970 (0.882–1.066)	0.527		
Smoking	0.921 (0.431–1.964)	0.831		
Hypertension	1.983 (0.967–4.068)	0.062	0.950 (0.365–2.475)	0.917
Diabetes mellitus	1.393 (0.635–3.055)	0.408		
Cardiovascular disease	1.635 (0.747–3.578)	0.219		
Cerebrovascular disease	1.221 (0.433–3.441)	0.706		
Liver disease	1.263 (0.546–2.923)	0.585		
Renal disease	2.122 (0.720–6.259)	0.173		
Malignancy	0.327 (0.037–2.878)	0.313		
WBC	1.160 (1.060–1.269)	0.001	1.138 (1.019–1.271)	**0.022**
NLR	1.037 (0.997–1.078)	0.072	0.976 (0.934–1.020)	0.284
D-dimer	1.054 (0.901–1.234)	0.510		
CRP	1.007 (1.002–1.011)	0.004	1.003 (0.998–1.009)	0.221
Procalcitonin	1.054 (0.941–1.180)	0.362		
PSI	1.020 (1.008–1.031)	0.001	0.993 (0.969–1.018)	0.568
CURB-65	2.089 (1.441–3.029)	< 0.001	2.291 (1.271–4.313)	**0.010**
HA	1.014 (1.006–1.022)	< 0.001	1.013 (1.003–1.022)	**0.011**

Notes: Odd ratio and 95% CI were calculated using univariate and multivariate logistic regression analysis. Bold text indicates P-value < 0.05.

Abbreviations: CAP, community-acquired pneumonia; SCAP, severe CAP; CI, confidence interval; BMI, body mass index; WBC, white blood cells; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; PSI, pneumonia severity index; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years old; HA, hyaluronic acid.

0.002). Comparatively, HA's predictive value for SCAP was not inferior to CURB-65 (Δ AUC: 0.010, 95% CI: −0.100–0.120, P = 0.860) or WBC (Δ AUC: −0.054, 95% CI: −0.176–0.067, P = 0.380).

To evaluate the collective predictive efficacy of HA, CURB-65, and WBC count, we developed a multivariate logistic regression model. The model is defined by the equation:

$$Y = -3.348 + 0.010*HA + 0.568*CURB\text{-}65 + 0.104*WBC.$$

This equation was derived to quantify the individual contributions of each parameter to the prediction of SCAP. Subsequent ROC analysis confirmed the superior predictive capacity of this composite model for SCAP, with an AUC of 0.800 (95% CI: 0.727–0.873, P < 0.001) (Figure 3, Table 3). This AUC value indicates a high discriminatory ability, suggesting that the model effectively distinguishes between patients who are at risk for SCAP and those who are not. Thus, HA may improve the diagnostic accuracy of SCAP by complementing existing indicators.

To assess the universality of HA as a diagnostic marker for SCAP, we expanded our analysis to include categorization of patients based on age, sex, BMI, smoking habits, comorbidities, and pathogens. ROC analyses were conducted to assess the predictive power of HA for SCAP across these subgroups. Our analysis indicated that HA showed predictive value for SCAP across various demographic groups. Although there were variations in the AUC values among subgroups, none of these differences reached statistical significance. This led us to preliminarily conclude that the predictive efficacy of HA for SCAP is not limited to specific groups but appears to be broadly applicable. Correlation analysis of the HA levels with clinical outcomes.

We explored the correlation between serum HA levels and clinical outcomes in patients with CAP. Patients were stratified based on the critical values derived from ROC curve analysis. Our findings indicated that the prevalence of SCAP was significantly higher among patients with elevated serum HA levels (54.3% vs 18.5%, P<0.001) (Figure 4A). Furthermore, a higher proportion of patients with high HA levels required hospitalization at 7 days (91.4% vs 64.6%, P<0.001) (Figure 4B). Regarding mortality rates, both the 30-day and overall mortality rates were markedly different between groups with varying

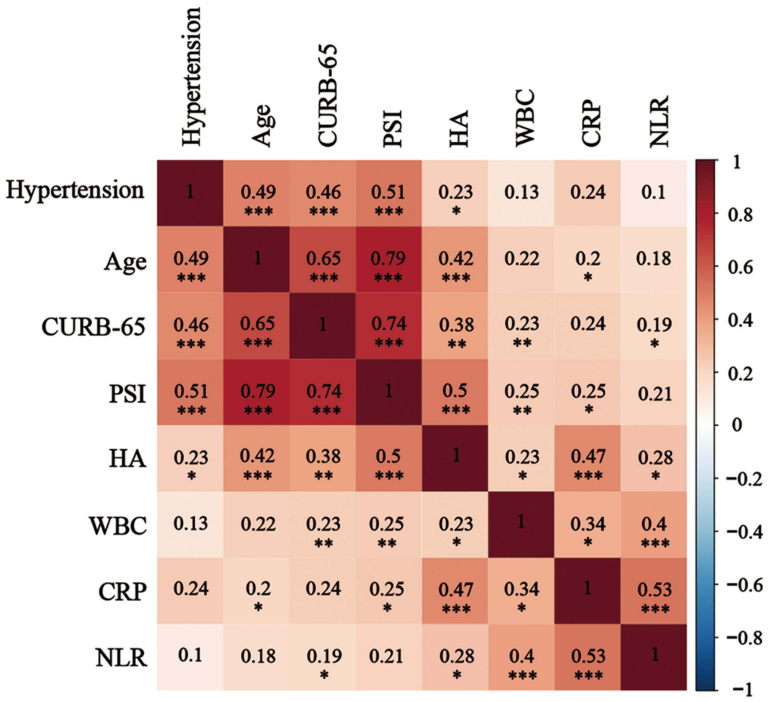

Figure 2 Correlation of HA levels with Different Variables.
Notes: *P < 0.05, **P < 0.01, ***P < 0.001.
Abbreviations: HA, hyaluronic acid; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years old; PSI, pneumonia severity index; WBC, white blood cells; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

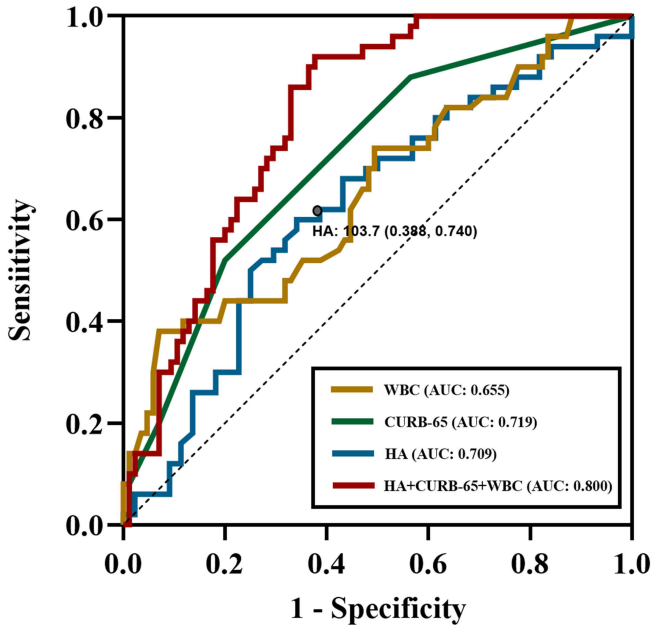

Figure 3 ROC curve analysis of various parameters for predicting SCAP.
Abbreviations: ROC, receiver operating characteristic; CAP, community-acquired pneumonia; SCAP, severe CAP; WBC, white blood cells; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years old; HA, hyaluronic acid; AUC, areas under the curve.

HA levels. Patients with lower HA levels exhibited significantly lower mortality rates compared to those with higher HA levels (Supplementary Figure 1). These results underscore the potential of HA levels as a prognostic biomarker for CAP, with higher levels being associated with increased severity and worse clinical outcomes.

Table 3 AUC and Thresholds for Predicting SCAP

	Threshold	Sensitivity (%)	Specificity (%)	AUC (95% CI)	P-value	Δ AUC (95% CI)	P-value
HA	103.7 ng/mL	74.0	61.2	0.709 (0.622, 0.797)	**0.001**	Reference	-
CURB-65	1.5	52.0	80.0	0.719 (0.635, 0.804)	**< 0.001**	0.010 (−0.100–0.120)	0.860
WBC	12 × 10^9/L	38.0	92.9	0.655 (0.228, 0.753)	**0.002**	−0.054 (− 0.176–0.067)	0.380
HA+CURB-65+WBC	-	92.0	62.4	0.800 (0.727, 0.873)	**< 0.001**	0.091 (0.021–0.160)	**0.010**

Notes: ROC analysis was conducted for HA, CURB-65, and HA+CURB-65+WBC. Bold text indicates P-value < 0.05.
Abbreviations: AUC, areas under the curve; CAP, community-acquired pneumonia; SCAP, severe CAP; ROC, receiver operating characteristic; CI, confidence interval; HA, hyaluronic acid; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years old; WBC, white blood cells.

Prognostic Power of HA Levels in Patients with CAP

Logistic regression analysis revealed that HA was an independent predictor of mortality in CAP patients (OR: 1.022, 95% CI: 1.005–1.039, P = 0.010) (Table 4). Additionally, Kaplan-Meier survival analysis revealed that CAP patients with higher HA levels had a significantly increased risk of 30-day mortality compared to those with lower HA levels (8.6% vs 1.5%, P = 0.008) (Figure 5). The correlation of HA levels with CAP severity and multiple clinical parameters suggests the potential of HA in monitoring CAP disease progression.

Power Analysis

To address potential concerns regarding the reliability of our study's findings due to sample size, we performed a post hoc power analysis. This analysis demonstrated that our study had a power of 98.857% in the two-sided z-test at a significance level of 0.05, enabling us to detect a difference of 0.2090 between the AUC value of 0.7090 under the null

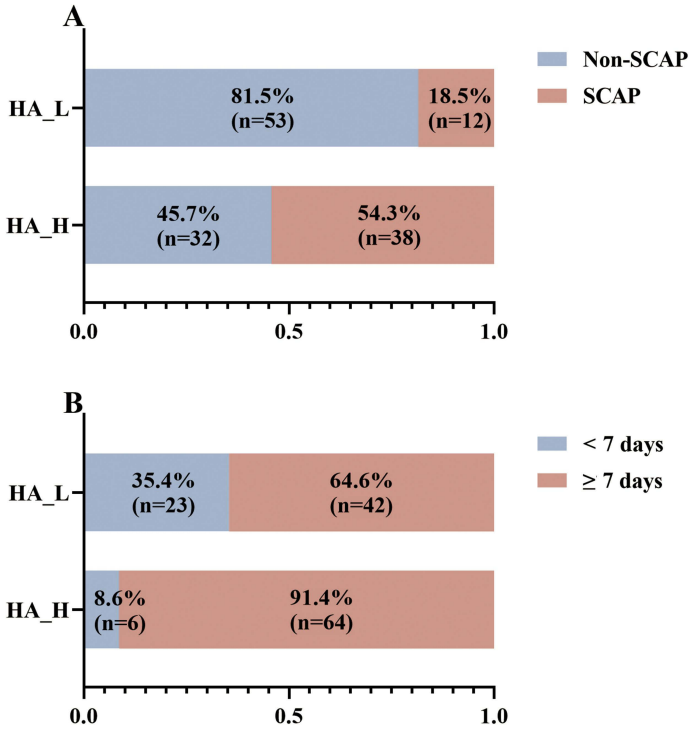

Figure 4 Distribution of prognostic outcomes based on the threshold of 103.7 ng/mL of HA. (**A**) Distribution of SCAP and non-SCAP among patients in different HA groups. (**B**) Distribution of hospitalization days in patients with different HA levels.
Abbreviations: HA, hyaluronic acid; CAP, community-acquired pneumonia; SCAP, severe CAP.

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Table 4 Risk Factors for Death in Patients with CAP

	Univariate Analysis		Multivariate Analysis	
	Odd ratio (95% CI)	**P-value**	**Odd ratio (95% CI)**	**P-value**
Age	1.044 (0.998–1.091)	0.059	0.997 (0.934–1.065)	0.938
Male	2.343 (0.594–99.250)	0.222		
BMI	0.865 (0.724–1.035)	0.113		
Smoking	1.293 (0.357–4.681)	0.695		
Hypertension	3.182 (0.883–11.471)	0.077	1.622 (0.307–8.564)	0.569
Diabetes mellitus	1.714 (0.470–6.252)	0.414		
Cardiovascular disease	2.611 (0.744–9.168)	0.134		
Cerebrovascular disease	4.879 (1.257–18.938)	0.022	2.697 (0.427–17.058)	0.292
Liver disease	0.343 (0.042–2.795)	0.317		
Renal disease	1.897 (0.369–9.746)	0.443		
Malignancy	2.380 (0.253–22.399)	0.448		
WBC	1.024 (0.901–1.163)	0.717		
NLR	1.005 (0.949–1.065)	0.857		
D-dimer	1.122 (0.933–1.348)	0.222		
CRP	1.000 (0.992–1.007)	0.963		
Procalcitonin	1.056 (0.933–1.194)	0.388		
PSI	1.033 (1.014–1.052)	0.001	0.995 (0.953–1.040)	0.838
CURB-65	2.686 (1.544–4.672)	< 0.001	3.082 (0.964–9.846)	0.058
HA	1.019 (1.007–1.030)	0.001	1.022 (1.005–1.039)	**0.010**

Notes: Odd ratio and 95% CI were calculated using univariate and multivariate logistic regression analysis. Bold text indicates P-value < 0.05.

Abbreviations: SCAP, severe community-acquired pneumonia; CI, confidence interval; BMI, body mass index; WBC, white blood cells; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; PSI, pneumonia severity index; CURB-65, confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years old; HA, hyaluronic acid.

hypothesis and the AUC value of 0.5000 under the alternative hypothesis. Consequently, the probability of failing to detect a true effect is only 1.143%, equating to a 98.857% confidence level in the significance of our results.

Discussion

CAP, a common community-acquired infection, is a leading cause of mortality due to infection and septic shock.[41,42] Approximately 20% of CAP are classified as SCAP,[2] and 40% of CAP patients require hospitalization.[43] The mortality for hospitalized CAP patients is as high as 15%.[44] Woodhead et al[45] reported an 11.3% higher mortality for CAP patients

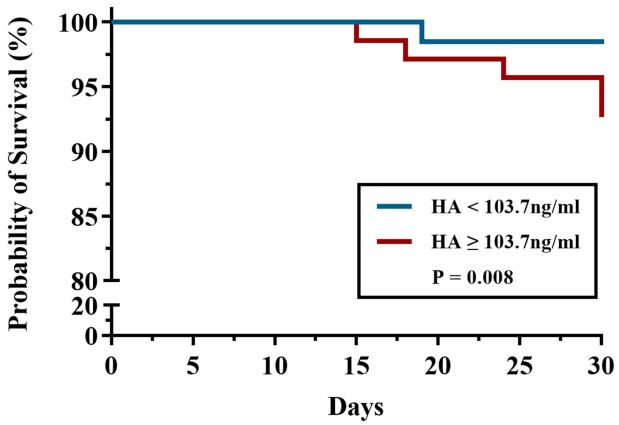

Figure 5 Kaplan-Meier analysis of 30-day mortality in patients with CAP stratified by HA.
Abbreviations: CAP, community-acquired pneumonia; HA, hyaluronic acid.

admitted to the ICU after the first week compared to those admitted within the first 48 hours. Hence, early recognition of SCAP is crucial for clinicians to make appropriate decisions and to improve the prognosis of patients with CAP.[46,47]

HA, a key component of the ECM,[48] has been linked to several pathological conditions, including organ fibrosis,[49] tumorigenesis,[50] and severe infections.[51,52] There is increasing evidence that HA plays a critical role in lung pathophysiology, particularly in the processes of inflammation and fibrosis.[53,54] Papakonstantinou et al[55] reported a significant increase in HA levels during exacerbations of COPD, correlating with airway remodeling and inflammation. In patients with ARDS, substantial accumulation of HA in the lungs has been implicated in the progression of interstitial and alveolar edema.[23] Recent studies have shown that HA levels are elevated in COVID-19, and HA is associated with the severity of lung infection.[29,30] However, the correlation between HA levels and the severity or prognosis of CAP remains unclear.

In the present study, we found significantly elevated HA levels in CAP patients compared to healthy controls. There was a significant positive correlation between serum HA levels and several inflammatory markers (WBC, CRP, and NLR), which are known biomarkers of infection progression and prognosis in CAP. Similar to our findings, Jiang et al[56] and Petrey et al[27] also reported elevated HA levels in inflammatory conditions. The inflammatory cascade response following pathogen attack may be responsible for elevated serum HA levels in CAP patients.[20] In addition, we found a positive correlation between HA levels and the severity of CAP, including respiratory failure, mechanical ventilation, infectious shock, prolonged hospital stays, and an increased incidence of ICU admission.

The CURB-65 score is a well-established clinical tool utilized to assess the severity of CAP.[57–59] However it is limited by poor specificity due to its limited number of indicators.[60] Some studies have even found that CURB-65 is biased in assessing the severity of viral pneumonia.[61] Our study's results demonstrated that the accuracy of HA in predicting SCAP was comparable to the CURB-65 score. Furthermore, the accuracy of predicting SCAP could be significantly improved by combining HA with CURB-65 and leukocyte counts. This suggests that HA can serve not only as a standalone marker for the rapid initial diagnosis of patients with CAP but also as a complement to existing diagnostic tools, thereby enhancing the accuracy of results when used in conjunction with CURB-65. This combined approach may offer a more comprehensive assessment, addressing the limitations of CURB-65 and improving the clinical management of CAP patients.

Previous research has documented elevated levels of HA during the progression of pulmonary lesions.[62] Yang et al[29] have shown that HA plays a role in the formation of ground-glass opacity and consolidation in mice. HA, known for its potent water-retaining properties,[63] can induce interstitial and alveolar edema.[23] This edema can worsen the clinical course of the disease by impairing gas exchange and lung function.[64] Our study observed a significant association between HA levels and lung lesions in patients with CAP, with a higher incidence of pulmonary consolidation, pleural effusion, and pulmonary infiltrates in the high HA group. Additionally, our findings identified HA as an independent predictor of mortality in CAP patients, with those exhibiting high HA levels experiencing significantly higher rates of both total and 30-day mortality. Consistent with our findings, elevated HA levels in COVID-19 patients have been correlated with a poor prognosis.[65] Inhibition of HA synthesis in COVID-19 patients has been shown to reduce lung lesions and improve patient prognosis.[29] These findings confirm the important role of HA in pulmonary pathophysiology and suggest that targeting HA synthesis and degradation may offer a novel therapeutic strategy for CAP.

Elevated HA levels have been observed in both viral and bacterial infections.[66,67] Our study found no significant difference in HA expression between different CAP pathogens. This phenomenon indicated that HA may act as a broad-spectrum biomarker for SCAP, rather than being specific to a certain pathogen. We hypothesize that the nonspecificity of HA for pathogens may be attributed to its role as a component of the endothelial glycocalyx.[13,14] Similarly, Syndecan-4, another constituent of the endothelial glycocalyx, has been observed to exhibit serum levels that are independent of the pathogen species.[9,68] Endothelial dysfunction, triggered by diverse pathological conditions, can lead to sloughing of the endothelial glycocalyx and consequent release of HA.[69] The increase in HA levels may thus serve as an indicator of the overall infectious burden within the host, rather than being limited to the effects of a specific pathogen. Previous studies on CAP have predominantly focused on bacterial etiologies,[70,71] with rare research comprehensively assessing bacteria, virus, and co-infections.[2] Our study addresses this gap by demonstrating the potential of HA as a novel and broad-spectrum inflammatory biomarker for CAP, offering the advancement of CAP diagnosis and providing new perspectives on the clinical management of CAP patients.

Power calculations were essential to ascertain whether our sample size was adequately powered to detect the correlation effect with confidence. The post hoc power analysis demonstrated a 98.857% certainty in the results of the current study. Consequently, given the sample conditions of this study, we can infer that HA has the potential to predict SCAP. Our study also calculated the optimal HA threshold for identifying SCAP to be 103.7 ng/mL. This threshold offers a practical basis for the clinical management of HA in patients with CAP. When the serum HA level is below 103.7 ng/mL in patients with CAP, outpatient follow-up treatment or admission to the hospital for general medical care may be considered on a case-by-case basis. Conversely, when the serum HA level exceeds 103.7 ng/mL in CAP patients, hospitalization is recommended for further evaluation as potential SCAP cases. In addition to this threshold, other necessary tests and comprehensive analyses are performed to target the management and monitoring of SCAP patients with the appropriate intensity of treatment.

We acknowledge that our study has several limitations that may affect the interpretation and generalizability of our results. Firstly, our study was conducted with a sample from a single hospital source during one season, which limits the diversity and size of our sample. This may, in turn, restrict the persuasiveness and applicability of our findings. Secondly, our assessment of the severity and short-term prognosis of CAP patients relied solely on serum HA levels at admission. The absence of long-term monitoring of HA levels prevents us from demonstrating the value of HA in tracking disease progression or treatment response, thereby limiting the clinical application of HA in outpatient settings and long-term monitoring. Additionally, our study investigated the diagnostic value of HA within the CAP population, but potential confounders may have influenced our assessment of the cause of elevated HA levels.

Therefore, to further elucidate the specific expression pattern and clinical value of HA in CAP, it is essential to conduct multicenter, multiseasonal studies involving large numbers of patients with respiratory infections, including CAP and other respiratory or inflammatory diseases, for cross-sectional comparisons. Longitudinal analyses at multiple time points and over extended periods are also necessary to provide a more comprehensive understanding of HA's role in disease management.

Conclusion

Our study provides evidence supporting an association between HA levels and disease severity in patients with CAP. HA demonstrates potential as an independent predictor of SCAP. Furthermore, the increase in HA levels appears to be pathogen-independent and exhibits universality across various etiologies. Consequently, HA holds promise as a valuable decision-making tool for clinicians in the management of CAP.

Data Sharing Statement

The data from this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Ethics Approval and Informed Consent

This study was approved by the ethics committee of Beijing Ditan Hospital (No. DTEC-KT2023-001-01). This study was conducted according to the Declaration of Helsinki and institutional guidelines. A waiver of informed consent was granted by the ethics committee due to a retrospective design of identified data and a minimal risk involved.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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