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ORIGINAL ARTICLE

Elevated Lactate, D-dimer, and IL-6 Associated with Elderly Community-Acquired SARS-CoV-2 Pneumonia Severity

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SUMMARY

Background: **Uncontrolled systemic inflammatory responses significantly contribute to the pathogenesis of severe community-acquired pneumonia (CAP) following SARS-CoV-2 infection (CASP). Elderly populations, being particularly vulnerable to respiratory infections, demonstrate both increased susceptibility to SARS-CoV-2 infection and greater disease severity. This study aimed to identify readily available routine hematological biomarkers that could serve as independent risk factors for predicting severe CASP (sCASP) in elderly patients.**
Methods: **A retrospective study was conducted to analyze 77 elderly people with CASP. According to the severity of the disease, the elderly people were divided into a non-sCASP group and a sCASP group, and the routine comprehensive laboratory examinations were compared.**
Results: **A total of 77 elderly patients with CASP were enrolled in this study, comprising 35 cases in the non-sCASP group and 42 cases in the sCASP group. Significant differences were observed in admission laboratory parameters, including routine blood counts, coagulation profiles, liver and kidney function tests, inflammatory markers, and composite laboratory-derived indices, between non-sCASP and sCASP cases infected with SARS-CoV-2 Omicron subvariants BA.5.2 and BF.7 ($p < 0.05$). Multivariate logistic regression and receiver operating characteristic (ROC) curve analyses identified lactate > 1.95 mmol/L, D-dimer > 0.85 mg/L, and IL-6 > 33.5 pg/mL as the most probable independent risk factors for sCASP in elderly patients. Notably, the combined diagnostic model (lactate-D-dimer-IL-6) demonstrated superior predictive performance for disease severity (AUC = 0.981; 95% CI: 0.954 - 1) compared to any single biomarker alone.**
Conclusions: **Elevated admission lactate, D-dimer, and IL-6 can be used as independent risk factors for the evaluation of CASP severity in elderly people, and the joint detection might be a better choice. This is imperative for guiding the development of effective interventions to alleviate severe patients' symptoms and burden.**
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INTRODUCTION

The main epidemiological characteristics of community-acquired acute respiratory infectious diseases include diverse respiratory pathogenic microorganisms and clinical manifestations, seasonal cycle, high contagion po-

tential and transmissibility, global pandemic potential, and vaccine prevention for only partial respiratory infections [1]. Importantly, community-acquired pneumonia (CAP) caused by a large variety of respiratory pathogenic bacteria, viruses, atypical microorganisms, fungi, and co-infections has made the most significant impact and has become the most significant challenge on the public health and a financial burden for healthcare systems; a significant cause of morbidity, hospitalizations, and mortality annually [2,3]. Particularly, it is the leading cause of death among the elderly population due to severe CAP (sCAP) [4]. The COVID-19 pandemic has also led to a significant enhancement in the people's perception and awareness regarding this topic [5].

The COVID-19 pandemic continues to be fueled by the emergence of highly infectious SARS-CoV-2 variants, maintaining its status as one of the most prevalent acute respiratory infectious diseases worldwide. This poses a significant threat, particularly to vulnerable populations such as the "one old and one young" (the elderly and young children) and immunocompromised individuals [6]. Remarkably, the persistent circulation of SARS-CoV-2 presents significant diagnostic challenges, as COVID-19's diverse clinical manifestations often overlap with those of other acute respiratory infections, complicating early differential diagnosis [7,8]. A range of molecular diagnostic techniques available include real-time reverse transcription polymerase chain reaction (RT-PCR), which is considered the gold standard for SARS-CoV-2 diagnosis [9]. However, there is an urgent need for accessible laboratory-based hematological diagnostic tools to complement RT-PCR testing, particularly when false-negative or false-positive results occur due to nasopharyngeal swab sampling limitations or technical constraints - a critical concern in emergency settings and resource-limited environments [10].

The human immune system is a critical factor in antiviral immunity and disease progression [11]. Emerging evidence indicates that SARS-CoV-2 infection triggers excessive pulmonary and systemic inflammation, mediated through both innate and adaptive immune pathways. This inflammatory cascade involves aberrant activation of nonspecific innate immune cells (particularly neutrophils and monocytes/macrophages) alongside dysfunctional adaptive immune responses characterized by lymphocyte exhaustion. These maladaptive immune mechanisms collectively contribute to the immunopathology underlying severe COVID-19 progression [12]. Early diagnosis and accurate assessment of disease severity are crucial for improving clinical outcomes in severe community-acquired pneumonia (sCAP) caused by SARS-CoV-2 infection (sCASP). However, considerable controversy persists regarding the risk factors and predictive value of various hematological parameters associated with CAP incidence, disease progression, and patient prognosis. This study, therefore, aimed to identify routinely available hematological biomarkers that may serve as independent risk factors for evaluating sCASP in elderly populations.

MATERIALS AND METHODS

Study population

This retrospective cohort study utilized data extracted from the hospital information system (HIS) of Tianjin Jinnan Hospital. The study protocol received ethical approval from the Institutional Review Board of Tianjin Jinnan Hospital (approval number: 2022-02) and was conducted in accordance with the Declaration of Helsinki. No informed consent was required due to the retrospective nature of the study. We enrolled elderly people hospitalized with acute lower respiratory tract infection symptoms and diagnosed with severe CAP from December 1, 2022, through October 31, 2023, in the Tianjin Jinnan Hospital. Inclusion criteria were age ≥ 60 years, subpleural patchy ground-glass opacities on chest high-resolution CT, and minimum one of the following symptoms: fever (≥ 38.0°C), cough, pleuritic chest pain, dyspnea, or focal chest signs on auscultation. Exclusion criteria were no SARS-CoV-2 detection, patients with primary immunodeficiency and secondary immunodeficiency, hospital-acquired pneumonia, and less than 24 hours of hospitalization.

Clinical data were recorded on admission

Within 24 hours of admission, the following clinical parameters were anonymously extracted from electronic medical records: demographic characteristics, laboratory data including complete blood count, coagulation parameters, biochemical parameters, trace elements, and inflammatory markers. The study incorporated the calculation of ten laboratory composite derived indexes as follows: NLR, absolute neutrophil count-to-absolute lymphocyte count ratio; PLR, platelet count-to-absolute lymphocyte count ratio; PMR, platelet count-to-absolute monocyte count ratio; MLR, absolute monocyte count-to-absolute lymphocyte count ratio; AISI, aggregate index of systemic inflammation (AISI = absolute neutrophil count x platelet count x absolute monocyte count/ absolute lymphocyte count); SII, systemic immune inflammation index (SII = platelet count x absolute neutrophil count/absolute lymphocyte count); SIRI, systemic inflammation response index (SIRI = absolute neutrophil count x absolute monocyte count/absolute lymphocyte count); NPAR, neutrophil percentage-to-albumin ratio; UAR, uric acid-to-albumin ratio; CLR, C reactive protein-to-absolute lymphocyte count ratio; and CPR, C reactive protein-to-procalcitonin ratio.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation and compared with a *t*-test. Non-normally distributed continuous variables were expressed as the median value (P25, P75), and the Mann-Whitney U rank sum test was used to compare the two groups. Categorical data were presented as n (%) and compared using a chi-squared test. The multivariate logistic analysis was performed using

the backward elimination method for covariates with $p < 0.05$ in the univariate analysis. The multivariate logistic regression model was constructed for factors with sCSAP. The receiver operating characteristic curve (ROC) was used for the cutoff value analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of demographic characteristics between non-sCASP group and sCASP group

A total of 77 elderly patients diagnosed with CASP were stratified into two groups: non-sCASP (n = 35) and sCASP (n = 42) (Figure 1). Baseline characteristic comparison revealed statistically significant differences in age and gender distribution between the groups ($p < 0.05$), as described in Supplemental Table S1.

Correlates between laboratory hematological parameters and disease severity in elderly people with CSAP

In the two CASP groups, we conducted an analysis of clinical laboratory hematological parameters and observed that most hematological parameters exhibited significantly distinct effects between the sCASP group and the non-sCASP group. Specifically, the variables analyzed included absolute white blood cell (WBC) count, absolute neutrophil (NEUT) count, prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, aspartate aminotransferase (AST), albumin (ALB), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, uric acid, lactate, calcium (Ca), iron (Fe), magnesium (Mg), phosphorus (P), C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6) ($p < 0.05$), as detailed in Supplemental Table S1.

Correlates between laboratory composite derived indexes and disease severity in elderly people with CSAP

In these two CASP groups, we conducted an analysis of clinically relevant laboratory-derived composite indexes and observed that various variables exhibited significantly distinct effects between the sCASP group and the non-sCASP group among elderly individuals. Specifically, the NLR, SII, SIRI, NPAR, UAR, and CLR values in the sCASP group were significantly higher than those in the non-sCASP group ($p < 0.05$), as detailed in Supplemental Table S2.

Results of univariate logistic regression analysis

The univariate analysis revealed that the following 23 independent variables were significantly different ($p < 0.05$): age and gender; WBC, NEUT, APTT, D-dimer, ALB, LDH, BUN, creatinine, uric acid, lactate, Ca, Fe, Mg, and P; inflammatory factors: CRP and IL-6; and laboratory composite derived indexes: NLR, SII, NPAR, UAR, and CLR, as described in Supplemental Table S3 and Figure 2.

Results of the multivariate logistic regression analysis

Subsequently, multicollinearity analysis was performed on all parameters that showed statistical significance in the univariate analysis. Variables with a variance inflation factor (VIF) > 10, namely WBC, NEUT, urea, uric acid, NLR, SII, UAR, and CLR, were excluded from further multivariate logistic regression analysis. The remaining 15 variables were included in the multivariable logistic regression model, which identified three independent predictors of sCASP ($p < 0.05$): lactate (OR: 115.203, 95% CI: 2.786 - 4,763.976, $p = 0.012$); D-dimer (OR: 5.541, 95% CI: 1.199 - 25.609, $p = 0.028$); and IL-6 (OR: 1.059, 95% CI: 1.004 - 1.117, $p = 0.035$). These findings indicate that elevated lactate, D-dimer, and IL-6 levels are independently associated with the development of sCASP, as illustrated in Figure 3.

Prediction of severity by ROC curves

Based on these findings, we propose that lactate, D-dimer, and IL-6 are clinically meaningful biomarkers for predicting the severity of CASP. Receiver operating characteristic (ROC) curve analysis demonstrated that lactate (AUC: 0.812, 95% CI: 0.719 - 0.904) had superior differentiating power in distinguishing elderly sCASP cases from non-sCASP cases compared to D-dimer (AUC: 0.769, 95% CI: 0.664 - 0.874) and IL-6 (AUC: 0.727, 95% CI: 0.615 - 0.838). The optimal cutoff values for predicting CASP severity were: lactate: 1.95 mmol/L; D-dimer: 0.85 mg/L; and IL-6: 33.5 pg/mL. Notably, the combination of all three biomarkers (lactate + D-dimer + IL-6) exhibited significantly enhanced diagnostic performance (AUC: 0.981, 95% CI: 0.954 - 1.000), outperforming any single marker alone (Figure 4).

DISCUSSION

As is well recognized, a defining clinical characteristic for COVID-19 is its unpredictable clinical course, which can rapidly deteriorate into sCASP [13]. With a significant improvement in the researchers' awareness regarding this topic, it is of practical significance to distinguish the severity of the disease by using derivative indicators [14]. Univariate analysis showed that NLR and SII were significantly associated with sCASP in elderly COVID-19 patients. Severe infection triggers a complex interplay between COVID-19-associated coagulopathy, ARDS, and multi-organ dysfunction [15]. Consistent with prior research [16,17], our multivariate analysis identified elevated admission lactate and D-dimer levels as independent risk factors for severe CASP in elderly patients. These findings support the clinical utility of admission lactate for disease severity assessment, while also underscoring the importance of monitoring D-dimer levels, given their parallel increase. Al-

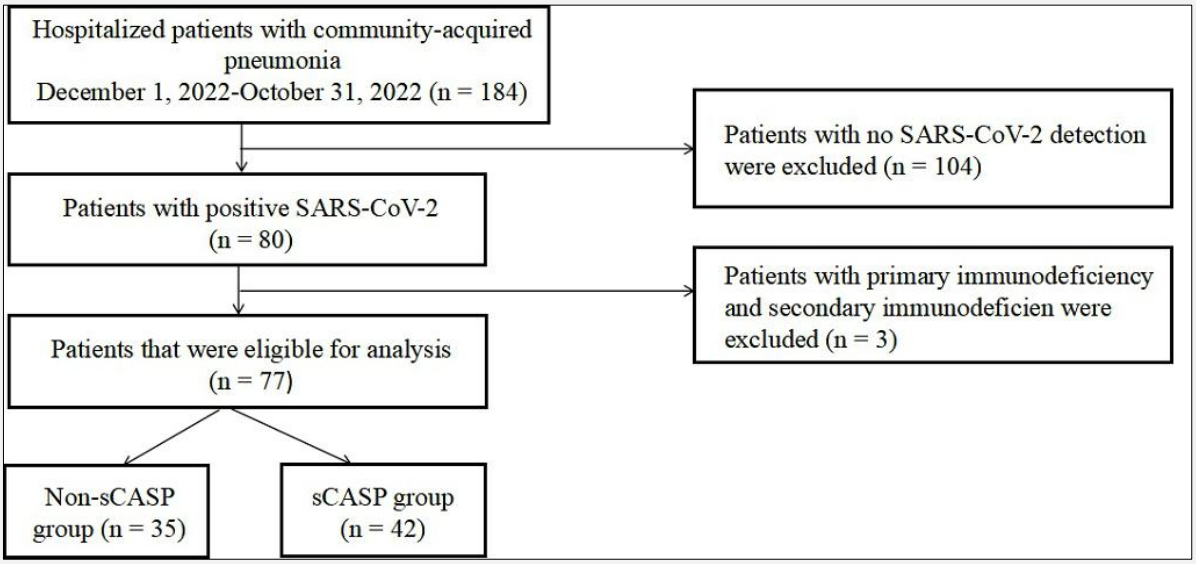

Figure 1. The flowchart of the study process.

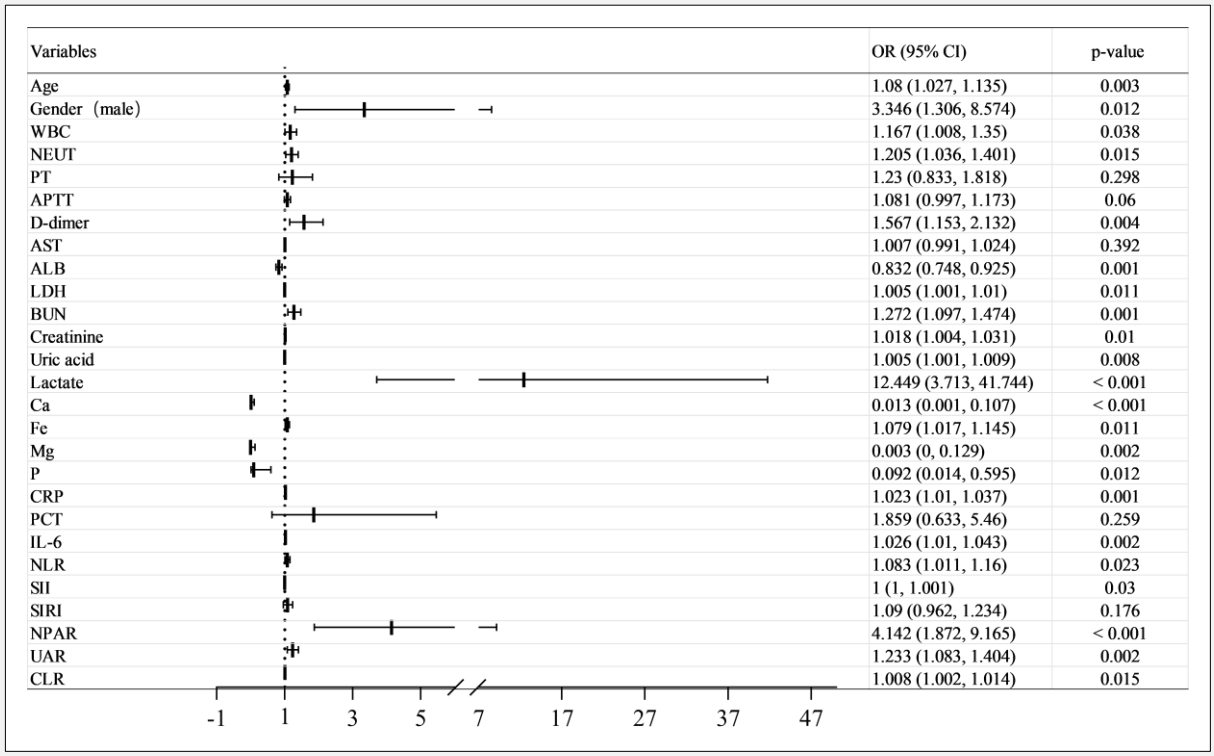

Figure 2. Forest plot of univariate logistic regression analysis for risk factors associated with sCASP on admission.

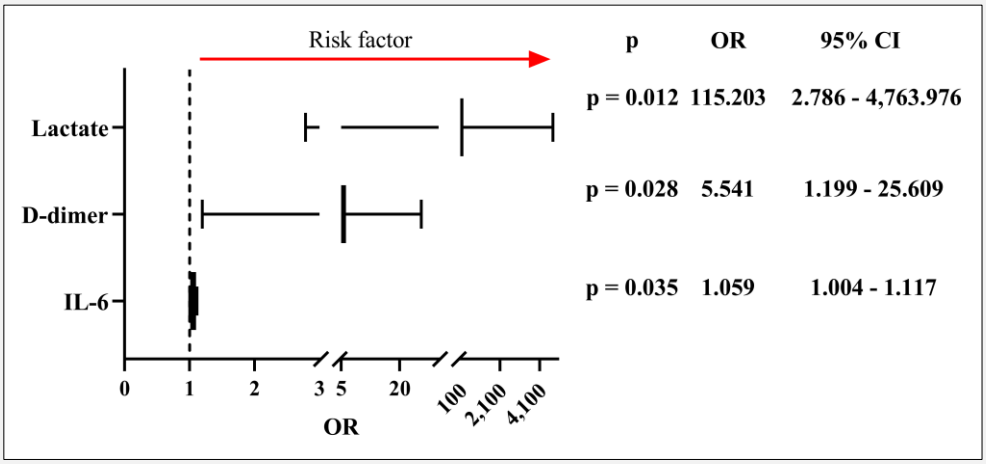

Figure 3. Forest plot of multivariate logistic regression analysis for risk factors associated with sCASP on admission.

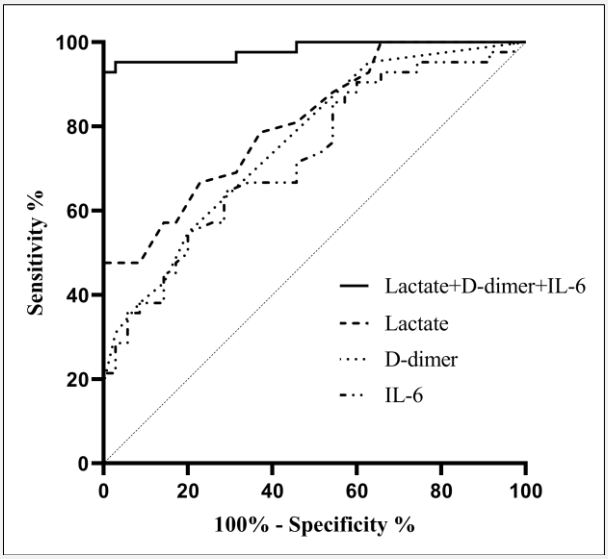

Figure 4. Receiver operator characteristic curve of sCASP and risk factors.

though univariate analysis revealed significant differences in both IL-6 and CRP levels between sCASP and non-sCASP groups, subsequent multivariate logistic regression confirmed admission IL-6 as the sole inflammatory marker independently predictive of severe outcomes. Our observation corresponds with the description made by Brandenburg et al. [18] and Mahmood et al. [19]. This highlights the importance of IL-6 as a prediction tool for not only assessing COVID-19 clinical outcomes but also monitoring the efficacy of anti-IL-6 treatment [20,21]. Remarkably, multiple studies have demonstrated a significant association between circulating trace element imbalances and COVID-19 disease severity and clinical outcomes [22,23]. Univariate logistic regression analysis revealed significant associations between lower calcium (Ca), phosphorus (P), magnesium (Mg) levels, and higher iron (Fe) levels, and sCASP. However, these associations lost statistical sig-

nificance in the multivariate analysis, suggesting that while trace element imbalances may characterize CASP patients, they are not independent risk factors. Regarding inflammatory biomarkers, AUROC analysis identified lactate as the most robust independent predictor for differentiating between elderly sCASP and non-sCASP cases. Additionally, taking accessibility into account, we combined these three biomarkers into one variable. This combined model demonstrated a significantly higher AUROC compared to any individual biomarker alone, suggesting that a multi-marker approach may improve the evaluation of sCASP and better inform on clinical decision-making. However, due to the limitations of our sample size and the retrospective design, further large-scale studies are needed to validate these findings.

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Declaration of Interest:
The authors declared that no competing interest exists.

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