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ORIGINAL ARTICLE

Association of the NLR, BNP, PCT, CRP, and D-D with the Severity of Community-Acquired Pneumonia in Older Adults

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SUMMARY

Background: **This study aimed to investigate the value of the neutrophil-to-lymphocyte ratio (NLR), B-type natriuretic peptide (BNP), and D-dimer (D-D) in predicting pneumonia severity in older adults with community-acquired pneumonia (CAP).**
Methods: **The retrospective study included older adults with CAP at the General Hospital of Northern Theater Command from January 2017 to December 2019. Patient demographic information and clinical characteristics were collected. Logistic multivariable analysis was used to analyze the factors associated with CAP severity. Receiver operating curve (ROC) analysis was used to evaluate the value of each biomarker in severity prediction.**
Results: **A total of 158 patients were included: 85 with mild-moderate CAP and 73 with severe CAP. The multivariable logistic analysis showed that CRP (OR = 1.011; 95% CI: 1.011 - 1.022; p = 0.039), BNP (OR = 1.003; 95% CI: 1.001 - 1.004; p = 0.001), D-D (OR = 1.289; 95% CI: 1.031 - 1.611; p = 0.026), and NLR (OR = 1.111; 95% CI: 1.011 - 1.222; p = 0.030) were independent factors associated with pneumonia severity. ROC analysis demonstrated the value of each biomarker in pneumonia severity prediction: CRP (AUC = 0.791, 95% CI: 0.720 - 0.861), BNP (AUC = 0.803, 95% CI: 0.649 - 0.806), D-D (AUC = 0.727, 95% CI: 0.734 - 0.872), and NLR (AUC = 0.817, 95% CI: 0.751 - 0.883). The positive and negative predictive values were 0.68 and 0.81 for CRP, 0.79 and 0.75 for BNP, 0.62 and 0.80 for D-D, and 0.80 and 0.76 for NLR.**
Conclusions: **CRP, BNP, D-D, and NLR might be helpful independent factors in predicting pneumonia severity in older adults with CAP.**
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KEYWORDS

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common infectious disease of the lower respiratory tract caused by various pathogens such as bacteria, viruses, and mycoplasma. CAP has the highest respiratory disease mortality rate and is a leading cause of death in China, with a mortality rate of 19 in 100,000 deaths per year [1]. CAP is more likely to afflict older adults than young adults, and its onset can be insidious [2]. Moreover, CAP also develops quickly in older adults and can

easily lead to septic shock and respiratory failure, both of which are life-threatening.

One in five patients with pneumonia admitted to the hospital will develop severe pneumonia and be admitted to the intensive care unit (ICU) for observation and even rescue [3]. Therefore, it is particularly important to judge and manage correctly the progression of the disease [4]. Clinically, CURB-65 scores are commonly used to assess pneumonia severity. However, physicians are advised to interpret CURB 65 scores carefully in older adults with CAP since even patients with low scores can progress quickly and experience death [5]. As the aging population is increasing in China and will only continue to rise at higher rates, it is imperative to develop biomarkers to assess CAP prognosis in older adults [6,7].

Procalcitonin (PCT), C-reactive protein (CRP), and white blood cell (WBC) levels are commonly used biochemical indicators for infection or sepsis in clinical practice [8]. Since no study has suggested a single indicator that can enable an accurate evaluation, finding the specific indicators to support diagnosis is the key to guiding the correct treatment [9]. The use of neutrophil-to-lymphocyte ratio (NLR), B-type natriuretic peptide (BNP), and D-dimer (D-D) has attracted attention in recent years for the evaluation of respiratory infection, but they remain understudied biomarkers [10]. NLR was first used to assess cancer patients, but studies showed that NLR is also correlated with pneumonia severity [11,12]. A recent study also implicated BNP in the inflammatory response [13]. While D-D is well known as a marker of fibrinolytic degradation [14], D-D also increases during respiratory infection [15].

Hence, this study aimed to evaluate the value of the NLR, BNP, and D-D for predicting pneumonia severity in older adults with CAP. The results could help improve the management of CAP.

MATERIALS AND METHODS

Study design and patients

The retrospective study included older adults with CAP admitted to the Department of Respiratory Medicine and Respiratory Intensive Care Unit (RICU) of the General Hospital of Northern Theater Command from January 2017 to December 2019. The inclusion criteria were 1) diagnosed with CAP according to the Guidelines for Diagnosis and Treatment of Adult Community-acquired Pneumonia in China (Version 2016) (9, 16), and 2) age ≥ 65. The exclusion criteria were 1) severe chronic liver or kidney disease, 2) blood disorders, suppressed immune system, malignant tumors, or suspected tuberculosis, 3) pulmonary embolism, venous thrombosis of the lower limbs, connective tissue disease, acute coronary syndrome, or acute cerebrovascular disease, or 4) incomplete clinical information. This study was approved by the Ethics Committee of the General Hospital of Northern Theater Command, approval number Y-(2021)-100. Informed consent was waived because of the retrospective nature of the study.

Biochemistry

Within 2 hours after the patient was admitted to the hospital and before applying any anti-infective drugs, the samples were collected under strict sterile operation and sent to the laboratory. The whole blood cell count and CRP (in serum) were determined immediately. Samples were centrifuged at 3,500 rpm for 10 minutes for D-D determination (in citrate samples) or at 3,000 rpm for 10 minutes for PCT and BNP testing (both in serum). Routine blood tests were performed using an LH780 blood cell analyzer (Beckman Coulter, Brea, CA, USA). CRP was assayed using an OPP biological detector (Ottoman-1000, Upper Bio-Tech, Shanghai, China). PCT was measured using a hyper i300 micro dot dry fluorescence analyzer (Micropoint Bioscience, Shenzhen, China). BNP was measured using an E601 chemiluminescence immunoassay system (Roche Diagnostics, Basel, Switzerland). D-D was determined using an automatic coagulation analyzer (Sisen Meikang, China). The reagents and controls were those recommended by the manufacturers. Quality control was performed as per the government's requirements. The reference ranges were 0.9 - 3.1 for NLR, 3.5 - 9.5 × 10^9/L for WBC, 1.8 - 6.3 × 10^9/L for neutrophils, 1.1 - 3.2 × 10^9/L for lymphocytes, 125 - 350 × 10^9/L for platelets, < 10 mg/L for CRP, < 300 pg/mL for BNP, and < 0.55 ng/mL for D-D.

Data collection

The age, gender, smoking history, underlying diseases, length of hospital stay, PCT, CRP, BNP, D-D, WBC, NLR, and platelet-to-lymphocyte ratio (PLR) of the patients were collected.

According to the Guidelines for Diagnosis and Treatment of Adult Community-acquired Pneumonia in China (Version 2016) [9], the primary diagnostic criteria for severe CAP are 1) the necessity of endotracheal intubation for mechanical ventilation and 2) the presence of septic shock, and use of vasoactive drugs after active fluid resuscitation. The secondary criteria are 1) 30 breaths or more per minute, 2) oxygenation index (PaO_2/FiO_2) ≤ 250 mmHg, 3) X-ray imaging shows infiltration of multiple lobes, 4) disturbance of consciousness or disorientation, 5) blood urea nitrogen is ≥ 7.14 mmol/L, and 6) systolic pressure < 90 mmHg with the necessity for active fluid resuscitation. Patients meeting at least one primary criterion and three or more secondary criteria were diagnosed with severe pneumonia.

Statistical analysis

SPSS 23.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous data conforming to the normal distribution were expressed as means ± standard deviations (SD) and analyzed using Student's *t*-test. Continuous data with a non-normal distribution were expressed as medians (interquartile ranges (IQRs)) and analyzed

Table 1. Baseline characteristics of older adults with mild-moderate and severe CAP.

Characteristic	Mild-moderate group (n = 85)	Severe group (n = 73)	p
Age (year) mean ± SD	76.66 ± 6.88	77.37 ± 7.89	0.546
Gender (male/female)	61/24	49/24	0.527
Smoking history	42 (49.4)	32 (43.8)	0.484
Diabetes	9 (10.6)	6 (8.2)	0.613
Hypertension	46 (54.1)	42 (57.5)	0.666
Coronary heart disease	10 (11.8)	8 (11.0)	0.874
Length of hospital stay (day) mean ± SD	11.94 ± 8.08	15.99 ± 10.55	0.007
PCT (ng/L) median (IQR)	0.07 (0.04,0.46)	1.24 (0.40,5.70)	< 0.001
CRP (mg/L) mean ± SD	74.25 ± 53.40	141.00 ± 72.57	< 0.001
BNP (pg/mL) mean ± SD	405.50 ± 313.13	871.23 ± 456.58	< 0.001
D-D (ng/mL) median (IQR)	0.92 (0.59,2.14)	2.26 (1.20,3.95)	< 0.001
WBC ($\times 10^9$/L) mean ± SD	11.63 ± 3.41	12.65 ± 4.57	0.120
NLR mean ± SD	9.02 ± 5.79	17.53 ± 8.78	< 0.001
PLR mean ± SD	286.61 ± 183.40	309.25 ± 185.91	0.444

PCT - procalcitonin, CRP - C-reactive protein, BNP - B type or brain natriuretic peptide, D-D - D-dimer peptide, WBC - white blood cell count, NLR - neutrophil-to-lymphocyte ratio, PLR - platelet-to-lymphocyte ratio.
The reference ranges were 0.9 - 3.1 for NLR, 3.5 - 9.5 × 10^9/L for WBC, 1.8 - 6.3 × 10^9/L for neutrophils, 1.1 - 3.2 × 10^9/L for lymphocytes, 125 - 350 × 10^9/L for platelets, < 10 mg/L for CRP, < 300 pg/mL for BNP, and < 0.55 ng/mL for D-D.

using the Mann-Whitney U test. Categorical data were expressed as n (%) and analyzed using the chi-squared test. Logistic multivariable analysis was used to investigate whether PCT, CRP, BNP, D-D, and NLR were independently associated with pneumonia severity. The predictive value was analyzed by receiver operating curve (ROC) analysis. p-values < 0.05 were considered statistically significant.

RESULTS

Baseline patient characteristics

A total of 158 CAP patients, aged 76.7 ± 6.9 years old on average, were included in this study, of which 73 were diagnosed with severe CAP. The average length of hospital stay was 11.94 ± 8.08 days for the mild-moderate CAP group and 15.99 ± 10.55 days for the severe CAP group (p = 0.007). There were no significant differences between the two groups in gender, smoking history, or the presence of underlying disease, hypertension, or coronary heart disease (Table 1). The severe group had significantly higher values of PCT (0.07 (0.04, 0.46) vs. 1.24 (0.40, 5.70) ng/L), p < 0.001), CRP (141.00 ± 72.57 vs. 74.25 ± 53.40 mg/L, p < 0.001), BNP (871.23 ± 456.58 vs. 405.50 ± 313.13 pg/mL, p < 0.001), D-D (0.92 (0.59, 2.14) vs. 2.26 (1.20, 3.95) ng/mL, p < 0.001), and NLR (17.53 ± 8.78 vs. 9.02 ± 5.79, p < 0.001) compared with the mild-moderate group.

Factors associated with severe pneumonia

Univariable and multivariable logistic analyses were performed to evaluate the association of PCT, CRP, BNP, D-D, and NLR with the severity of CAP as the dependent variable. The multivariable analysis showed that CRP (OR = 1.011; 95% CI = 1.001 - 1.022; p = 0.039), BNP (OR = 1.003; 95% CI = 1.001 - 1.004; p = 0.001), D-D (OR = 1.289; 95% CI = 1.031 - 1.611; p = 0.026), and NLR (OR = 1.111; 95% CI = 1.011 - 1.222; p = 0.030) were all independently associated with pneumonia severity.

Table 2. Univariable and multivariable analyses of risk factors for severe CAP.

Characteristic	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Age (year)	1.013	0.971 - 1.058	0.543			
Gender (male vs. female)	0.803	0.407 - 1.585	0.527			
Smoking history	1.251	0.668 - 2.345	0.484			
Diabetes	0.227	0.098 - 0.528	0.001	0.172	0.050 - 0.589	0.005
Hypertension	0.871	0.463 - 1.635	0.667			
Coronary heart disease	0.471	0.175 - 0.951	0.038	0.261	0.064 - 1.069	0.131
PCT (ng/L)	3.187	1.818 - 5.588	0.000	1.529	0.093 - 2.560	0.106
CRP (mg/L)	1.018	1.011 - 1.025	0.000	1.011	1.001 - 1.022	0.039
BNP (pg/mL)	1.003	1.002 - 1.004	0.000	1.003	1.001 - 1.004	0.001
D-D (ng/mL)	1.336	1.115 - 1.601	0.002	1.289	1.031 - 1.611	0.026
WBC ($\times 10^9$/L)	1.067	0.985 - 1.155	0.114			
NLR	1.197	1.121 - 1.278	0.000	1.111	1.011 - 1.222	0.030
PLR	1.001	0.999 - 1.002	0.441			

PCT - procalcitonin, CRP - C-reactive protein, BNP - B type or brain natriuretic peptide, D-D - D-dimer peptide, WBC - white blood cell count, NLR - neutrophil-to-lymphocyte ratio, PLR - platelet-to-lymphocyte ratio.

Table 3. ROC analysis for the prediction of CAP severity.

Characteristic	AUC	p	95% CI	Sensitivity	Specificity	Cutoff value	PPV	NPV
CRP	0.791	< 0.001	0.720 - 0.861	0.822	0.671	80.50	0.68	0.81
BNP	0.803	< 0.001	0.734 - 0.872	0.705	0.847	672.35	0.79	0.75
D-D	0.727	< 0.001	0.649 - 0.806	0.836	0.565	1.01	0.62	0.80
NLR	0.817	< 0.001	0.751 - 0.883	0.700	0.847	12.10	0.80	0.76

CRP - C-reactive protein, BNP - B type or brain natriuretic peptide, D-D - D-dimer peptide, NLR - neutrophil-to-lymphocyte ratio, PPV - positive predictive value, NPV - negative predictive value.

ROC analysis results

The ROC analyses showed that CRP (AUC = 0.791, 95% CI: 0.720 - 0.861; 82.2% sensitivity and 67.1% specificity using a cutoff of 80.50 mg/L), BNP (AUC = 0.803, 95% CI: 0.649 - 0.806; 70.5% sensitivity and 84.7% specificity using a cutoff of 672.35 pg/mL), D-D (AUC = 0.727, 95% CI: 0.734 - 0.872; 83.6% sensitivity and 56.5% specificity using a cutoff of 1.010 ng/mL), and NLR (AUC = 0.817, 95% CI: 0.751 - 0.883; 70.0% sensitivity and 84.7% specificity using a cutoff of 12.10) had a certain value in predicting pneumonia severity (Table 3 and Figure 1). The positive and negative predictive values were 0.68 and 0.81 for CRP, 0.79 and 0.75 for BNP, 0.62 and 0.80 for D-D, and 0.80 and 0.76 for NLR.

DISCUSSION

This study suggests that CRP, NLR, BNP, and D-D are independently associated with the severity of CAP in older adults. It is clinically significant because older adults are at increased risk for CAP and the onset of CAP is often insidious, with quick progression to serious morbidity and mortality.

As science and technology develop, the average life span of humans extends with it, sharply increasing the proportion of older adults in the population. CAP mainly affects children and older adults, with older adults being at increased risk due to (1) weakened defense mechanisms and immune system (decreased innate immune function in the respiratory tract, including reduced mucous secretions, mucosal atrophy, decreased mucosal ciliary activity, weakened cough reflex, respi-

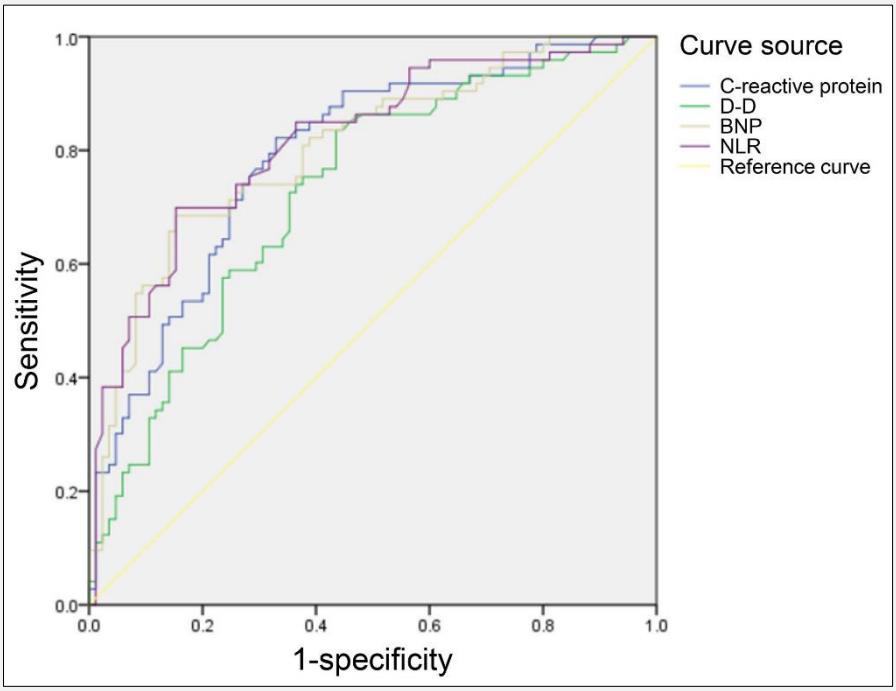

Figure 1. ROC curve analysis of CRP, BNP, D-D, and NLR.

ratory muscular atrophy, and poor pulmonary compliance; moreover, the immune function of T cells and B cells weakens with age) [16], (2) aspiration due to disease and improper nursing (older adults can have difficulty swallowing, and over 70% of patients with cerebral infarction, gastroesophageal reflux disease or oral disease experience aspiration) [17,18], and (3) many underlying diseases, with multiple damaged organ systems and poor nutrition. In addition, long-term and repeated infections can lead to long-term and repeated antibiotic use, thus resulting in drug resistance.

A study showed that over half of older adults with CAP had to be hospitalized for treatment, with 10% requiring admission to the intensive care unit (ICU) due to disease deterioration [19]. CAP can develop quickly in older adults, and progression to severe pneumonia is likely due to various factors. The mortality rate of severe pneumonia may be as high as 20% [20]. Hospitalization expenses are also a serious concern to the patients and their families. According to Raut et al. [21], the fixed daily expense of hospitalization accounted for 59% of total inpatient costs. Our study showed that patients with severe CAP had significantly longer hospital stays. Therefore, early evaluation and diagnosis are essential to prevent disease deterioration and reduce hospitalization expenses.

Whole blood cell count examinations, as one of the most common laboratory methods in clinical practice, are usually used for the preliminary evaluation of disease progression. WBC, neutrophil, and lymphocyte counts are commonly used to evaluate infections. Florin et al. [22] concluded that WBC counts were insufficient to evaluate the severity of CAP. Although counts rise during the early inflammatory response, they drop in severely infected patients because of suppressed immunity. Accordingly, this study demonstrated no significant differences in WBC counts between the severe and mild-moderate groups, further suggesting that WBC was unsuitable for evaluating pneumonia severity.

While NLR was first used in cancer patients, it was later found useful for evaluating cardiovascular diseases and acute pancreatitis [23]. Our study, showed that it could also be an ideal indicator to evaluate CAP severity. The results showed that there was a significant difference in NLR between the severe (17.527 ± 8.775) and mild-moderate (9.021 ± 5.785) groups ($p < 0.05$), suggesting that NLR was superior to WBC in pneumonia patients. Neutrophils increase because stem cells are stimulated by neutrophil demarginalization and granulocyte stimulating factors, while lymphocytes decrease due to apoptosis, marginalization, and redistribution [24], with the gap between neutrophils and lymphocytes proportional

to disease severity. The analysis of the area under the ROC curve showed that the cutoff value of NLR was 12.100, with decent sensitivity (70.0%) and specificity (84.7%). Since it is easy to measure and carries a low cost [25], it might be more convenient to use in grassroots institutions and clinics.

BNP is a peptide produced by the contraction and stretching of ventricular muscle cells under cardiac strain. BNP has a strong vasodilatory and antihypertensive effect and is important in regulating body fluid volume, vascular pressure, and electrolyte balance [26]. It is commonly used in cardiovascular medicine to evaluate heart failure and cardiac functions but was seldom reported in studies evaluating the severity of inflammation. This study showed a significant difference in BNP between the patients with severe and mild-moderate CAP, possibly due to the increased secretion of pro-inflammatory factors in severe pneumonia [27]. Like Li et al. [28], the logistic analysis also proved that BNP was an independent factor for severe pneumonia, with a higher BNP level indicating more severe pneumonia. According to the ROC curve, the accuracy of severity evaluation was the highest when BNP was above 672.35 pg/mL. It might be due to increased exudates in the pulmonary alveoli, causing pulmonary alveoli congestion, edema, and reduced oxygen exchange into the blood. It increases the secretion of inflammatory substances and hypoxia, leading to vasoconstriction and greater cardiac ejection resistance, leading to altered hemodynamics and increased BNP secretion by cardiomyocytes [29]. Together with other indicators measuring BNP, it can provide a more comprehensive evaluation of disease progression.

D-D is the smallest fragment produced from the fibrous protein degradation process and results from the joint action of activated thrombin, factor VIII, and fibrinolytic enzyme. Therefore, it reflects the activation of coagulation and fibrinolytic systems. Many foreign studies showed that D-D plays a significant role in diagnosing thrombosis, cardiovascular diseases, and tumors [30-31]. In this study, the severe group had a significantly greater D-D than the mild-moderate group, possibly due to a coagulation system disorder caused by an aggressive inflammatory response [32]. The logistic analysis in this study also proved that D-D was an independent influencing factor for severe pneumonia, similar to Liu et al. [33].

Severe pneumonia often causes dyspnea, which produces inflammatory factors that directly destroy vascular endothelial cells in a hypoxic environment. It results in coagulation system activation from exposed collagen and leads to hypercoagulability. As the infection continues and microthrombosis forms, severe pneumonia can cause severe shock and disseminated intravascular coagulation [34]. The ROC curve in this study showed that D-D had high sensitivity (83.6%) but low specificity (56.5%), in accordance with Snijders et al. [35]. However, others suggested that D-D should not be used alone to evaluate the severity of CAP since D-D increases with age. If used with other indicators in clinical application, D-D can be prognostic for pneumonia severity.

PCT plays a pivotal role in the diagnostic and therapeutic management of bacterial infectious diseases in clinical settings. The single-factor analysis revealed a notable discrepancy in PCT levels between the two groups, demonstrating statistical significance. However, in the multivariate analysis no statistically significant association was observed. Therefore, a ROC analysis was not conducted for PCT. This outcome may suggest that the intricate interplay of multiple variables might have hindered the manifestation of PCT's significance within this particular model. Additionally, it is worth noting that the limited number of cases involving severe CAP patients with concomitant sepsis caused by gram-negative bacilli might have contributed to this outcome. Notably, the latter group exhibited more pronounced variations in PCT values. The inclusion of a larger sample size in the multivariate analysis may yield statistically significant findings.

The limitations of this study include its design as a single-center retrospective study with a relatively small sample size, subject to geographical limitations. In addition, this study did not carry out a stratified analysis and did not further compare the patients in a quantitative manner. Finally, random partitioning or bootstrapping of the sample dataset could have increased the power of the ROC analysis by providing external validation of the data.

This study mainly identified abnormalities in biochemical markers in the early stage of CAP in older adults. If the test indicators exceed their threshold (calculated by the ROC curve), the patient’s condition might become more severe, and treatment should be given in time to prevent deterioration. Since this study was carried out on outpatients in the emergency department, the results were obtained in about 2 hours, which is helpful for clinicians to judge the patient’s condition. The advantage lies in its convenience and rapidity, which is more objective than the current clinical scoring systems.

In conclusion, CRP, BNP, D-D, and NLR were all independent prognostic factors for pneumonia severity. The biomarkers might help predict pneumonia severity in older adults with CAP.

Ethical Approval:

This study was approved by the Ethics Committee of the General Hospital of Northern Theater Command, approval number Y-(2021)-100. Informed consent was waived because of the nature of the retrospective study.

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Declaration of Interest:
The authors declare no conflict of interest.

References:

1. Zhou M, Wang H, Zhu J, et al. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet 2016; 387(10015):251-72. (PMID: 26510778)

2. Simonetti AF, Viasus D, Garcia-Vidal C, Carratala J. Management of community-acquired pneumonia in older adults. Ther Adv Infect Dis 2014;2(1):3-16. (PMID: 25165554)

3. Confalonieri M, Kodric M, Santagiuliana M, et al. To use or not to use corticosteroids for pneumonia? A clinician's perspective. Monaldi Arch Chest Dis 2012;77(2):94-101. (PMID: 23193846)

4. Stupka JE, Mortensen EM, Anzueto A, Restrepo MI. Community-acquired pneumonia in elderly patients. Aging health 2009; 5(6):763-74. (PMID: 20694055)

5. Parsonage M, Nathwani D, Davey P, Barlow G. Evaluation of the performance of CURB-65 with increasing age. Clin Microbiol Infect 2009;15(9):858-64. (PMID: 19702590)

6. Chen L, Huang H, Chen X. Distribution of Pathogens in Elderly Chinese Patients With Pneumonia: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2021;8:584066. (PMID: 34381791)

7. Chen L, Zhou F, Li H, et al. Disease characteristics and management of hospitalised adolescents and adults with community-acquired pneumonia in China: a retrospective multicentre survey. BMJ Open 2018;8(2):e018709. (PMID: 29449294)

8. Magrini L, Gagliano G, Travaglino F, et al. Comparison between white blood cell count, procalcitonin and C reactive protein as diagnostic and prognostic biomarkers of infection or sepsis in patients presenting to emergency department. Clin Chem Lab Med 2014;52(10):1465-72. (PMID: 24803611)

9. Qu JM, Cao B. [Guidelines for the diagnosis and treatment of adult community acquired pneumonia in China (2016 Edition)]. Zhonghua jie he he hu xi za zhi 2016;39(4):241-2. (PMID: 27117069)

10. Liu J, Tu C, Zhu M, et al. The clinical course and prognostic factors of severe COVID-19 in Wuhan, China: A retrospective case-control study. Medicine (Baltimore) 2021;100(8):e23996. (PMID: 33663044)

11. de Jager CP, Wever PC, Gemen EF, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PLoS One 2012;7(10):e46561. (PMID: 23049706)

12. Lee H, Kim I, Kang BH, Um SJ. Prognostic value of serial neutrophil-to-lymphocyte ratio measurements in hospitalized community-acquired pneumonia. PLoS One 2021;16(4):e0250067. (PMID: 33857241)

13. Man LL, Liu F, Wang YJ, et al. The HMGB1 signaling pathway activates the inflammatory response in Schwann cells. Neural Regen Res 2015;10(10):1706-12. (PMID: 26692874)

14. Tita-Nwa F, Bos A, Adjei A, Ershler WB, Longo DL, Ferrucci L. Correlates of D-dimer in older persons. Aging Clin Exp Res 2010;22(1):20-3. (PMID: 20305364)

15. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. J Thromb Thrombolysis 2020;50(3):548-57. (PMID: 32524516)

16. Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. J Clin Invest 2013;123(3):958-65. (PMID: 23454758)

17. Sura L, Madhavan A, Carnaby G, Crary MA. Dysphagia in the elderly: management and nutritional considerations. Clin Interv Aging 2012;7:287-98. (PMID: 22956864)

18. Cohen DL, Roffe C, Beavan J, et al. Post-stroke dysphagia: A review and design considerations for future trials. Int J Stroke 2016;11(4):399-411. (PMID: 27006423)

19. Almirall J, Serra-Prat M, Bolíbar I, Balasso V. Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration 2017;94(3):299-311. (PMID: 28738364)

20. Schöll N, Rohde GGU. [Community-acquired Pneumonia in the Elderly]. Pneumologie 2019;73(10):605-16. (PMID: 31622999)

21. Raut M, Schein J, Mody S, Grant R, Benson C, Olson W. Estimating the economic impact of a half-day reduction in length of hospital stay among patients with community-acquired pneumonia in the US. Curr Med Res Opin 2009;25(9):2151-7. (PMID: 19601711)

22. Florin TA, Ambroggio L, Brokamp C, et al. Biomarkers and Disease Severity in Children With Community-Acquired Pneumonia. Pediatrics 2020;145(6):e20193728. (PMID: 32404432)

23. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Rev Cardiovasc Ther 2016;14(5):573-7. (PMID: 26878164)

24. Djordjevic D, Rondovic G, Surbatovic M, et al. Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Mean Platelet Volume-to-Platelet Count Ratio as Biomarkers in Critically Ill and Injured Patients: Which Ratio to Choose to Predict Outcome and Nature of Bacteremia. Mediators Inflamm 2018. 2018: 3758068. (PMID: 30116146)

25. Langenickel T, Pagel I, Höhnel K, Dietz R, Willenbrock R. Differential regulation of cardiac ANP and BNP mRNA in different stages of experimental heart failure. Am J Physiol Heart Circ Physiol 2000;278(5):H1500-6. (PMID: 10775127)

26. Christ-Crain M, Breidthardt T, Stolz D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. J Intern Med 2008;264(2):166-76. (PMID: 18298480)

27. Seo H, Cha SI, Shin KM, et al. Clinical Impact of N-Terminal Prohormone of Brain Natriuretic Peptide on Patients Hospitalized with Community-Acquired Pneumonia. Am J Med Sci 2020; 360(4):383-91. (PMID: 32690276)

28. Li W, Ding C, Yin S. Severe pneumonia in the elderly: a multivariate analysis of risk factors. Int J Clin Exp Med 2015. 8(8): 12463-75. (PMID: 26550157)

29. Bezati S, Velliou M, Ventoulis I, Simitsis P, Parissis J, Polyzogopoulou E. Infection as an under-recognized precipitant of acute heart failure: prognostic and therapeutic implications. Heart Fail Rev 2023. 28(4): 893-904. (PMID: 36897491)

30. Smith A, Patterson C, Yarnell J, Rumley A, Ben-Shlomo Y, Lowe G. Which hemostatic markers add to the predictive value of conventional risk factors for coronary heart disease and ischemic stroke? The Caerphilly Study. Circulation 2005;112(20):3080-7. (PMID: 16286603)

31. Ay C, Vormittag R, Dunkler D, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol 2009;27(25):4124-9. (PMID: 19636003)

32. Gralinski LE, Sheahan TP, Morrison TE, et al. Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis. mBio 2018;9(5):e01753-18. (PMID: 30301856)

33. Huang X, Li D, Liu F, Zhao D, Zhu Y, Tang H. Clinical significance of D-dimer levels in refractory Mycoplasma pneumoniae pneumonia. BMC Infect Dis 2021. 21(1): 14. (PMID: 33407216)

34. Cerda-Mancillas MC, Santiago-Germán D, Andrade-Bravo B, et al. D-dimer as A Biomarker of Severity and Adverse Outcomes in Patients with Community Acquired Pneumonia. Arch Med Res 2020. 51(5): 429-435. (PMID: 32402575)

35. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. Eur J Intern Med 2012;23(5):436-41. (PMID: 22726372)