A new haematological model for the diagnosis and prognosis of severe community-acquired pneumonia: a single-center retrospective study

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Background: Severe community-acquired pneumonia (sCAP) is a condition where infection-induced lung tissue inflammation intensifies to a certain stage, resulting in organ dysfunction and even life-threatening disease. When sCAP occurs, neutrophils and monocytes will be activated and released into the peripheral blood to kill bacteria. There are significant morphological changes in these activated neutrophils and monocytes. Haematological parameters can reflect these morphological changes, and indicate the occurrence of sCAP and the severity of infection. This study is designed to establish a new haematological model and explore its clinical value in the diagnosis and prognosis of sCAP.

Methods: Patients who fulfilled the diagnostic criteria of common pneumonia (CP) and sCAP were enrolled in this study. Healthy body check-up patients were also enrolled as a control group. Characteristic information and 28-day survival of patients were recorded. Haematological results, C-reactive protein (CRP) and procalcitonin (PCT) were calculated by BC-6800 Plus automated haematology analyser and cobas E601 automated biochemical immunoassay analyser.

Results: A total of 100 check-ups patients, 100 CP patients, and 111 sCAP patients were enrolled in this study. The new haematological model WBC & Mon-XW, combining WBC (white blood cell count) and Mon-XW (monocytes complexity distribution width), was significantly elevated in the sCAP group and significantly higher than in the control group and the CP group. The new model had good diagnostic efficacy for sCAP, with an area under the receiver operating characteristic curve (ROC-AUC) of 0.842, which was higher than that of CRP (0.633) and PCT (0.750). Moreover, WBC & Mon-XW was effective for survival prognostic evaluations of sCAP, with an ROC-AUC of 0.748. The new model was the independent predictors for the death of pneumonia with an OR (odds ratio) value of 1.82. The 28-day mortality rate was approximately 40% in the WBC & Mon-XW ≥8.9 group, which was approximately 15% higher than that in the WBC & Mon-XW <8.9 group.

Conclusions: The new haematological model can be used as an indicator for sCAP diagnosis and prognosis.

Keywords: Severe community-acquired pneumonia (sCAP); complete blood count (CBC); haematological parameter; diagnosis; prognosis

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Introduction

Severe community-acquired pneumonia (sCAP) is a condition in which lung tissue (bronchioles, alveoli, and interstitium) inflammation intensifies, resulting in organ dysfunction and even life-threatening diseases (1). sCAP is mainly caused by infection resulting in difficulty breathing, shortness of breath, fever, and tachycardia, and is a leading cause of death from infectious disease worldwide. Patients with sCAP often require intensive care unit (ICU) care, and approximately 25% of these require invasive mechanical ventilation (2). One study showed sCAP patients admitted to ICU had a mortality rate of 35–58%, and was higher with longer ICU stays (3). As a critical condition, sCAP can easily lead to hydration, electrolyte imbalance, and pH problems if left untreated, resulting in multiple organ dysfunction and severe complications including septic shock (4). Therefore, early diagnosis and timely evaluation of the treatment response and prognosis are important role reducing the mortality rate and improving patient outcomes.

Some recent studies analysed different risk factors for sCAP, including age, difficulty swallowing, difficulty breathing, mechanical ventilation, and diabetes (5-9), and established clinical predictive models for its early diagnosis (10-13). However, most risk factors and clinical predictive models are based on clinical findings and clinical symptoms, which are often atypical in patients with sCAP (14,15), affecting their accuracy. While C-reactive protein (CRP), procalcitonin (PCT), and microbial culture are widely used as auxiliary diagnoses of infection, their sensitivity and specificity is relatively low (16-17), as is that of chest imaging, a common clinical approach (18). Therefore, clinicians need a more accurate, objective, and easy-to-use auxiliary diagnostic indicator for the disease. In addition to the infection biomarkers described above, established pneumonia severity assessments include the CURB (confusion, urea, respiratory rate, blood pressure) score, the pneumonia severity index (PSI) score, the Acute Physiology and Chronic Health Evaluation (APACHE) score, the Sequential Organ Failure Assessment (SOFA) score, the Multiple Organ Dysfunction Score (MODS) system, and the PIRO (predisposition, insult, response, organ dysfunction) score. CURB, PSI, and PIRO are used to predict the mortality rate and assess the risk of death, and APACHE, SOFA, and MODS are used to assess the condition and prognosis of critically ill patients, especially those with sepsis. These systems rely on a large amount of medical information, such as underlying physiological status, clinical symptoms, signs, complete blood count (CBC), biochemistry, immunity, imaging, and medications, which complicates the acquisition of complete information for daily assessments.

sCAP is inflammation of the lung tissue caused by infection. When sCAP occurs, neutrophils and monocytes, as the first responders against infection, will be activated and released into the peripheral blood in large quantities to kill bacteria. There are significant morphological differences between activated and non-activated neutrophils and monocytes, such as cell volume, internal complexity and nuclear density. With the development of haematological analyser in recent years, such morphological differences can be identified by haematological analyser and expressed in the form of haematological parameters. Therefore, haematological parameters can reflect the morphological changes of peripheral blood cells, and indicate the occurrence of sCAP and the severity of infection.

The haematological parameters evaluated in this study including cell populations of Neu and Mon, which provide information related to cell complexity, fluorescence intensity and distribution width on DIFF (Differential) channel. The following parameters are reported on the X-axis of DIFF channel scatter-gram: neutrophils cell complexity (Neu-X), monocytes cells complexity (Mon-X), neutrophils complexity distribution width (Neu-XW), and monocytes complexity distribution width (Mon-XW); whereas the following parameters are reported on the y-axis of DIFF channel scatter-gram: neutrophils fluorescence intensity (Neu-Y), monocytes fluorescence intensity (Mon-Y), neutrophils fluorescence intensity distribution width (Neu-YW), monocytes fluorescence intensity distribution width (Mon-YW).

Haematological parameters have been proposed as diagnostic and prognostic indicators for sepsis in recent studies (19-24). However, few studies have focused on the diagnostic and prognostic value of haematological parameters for sCAP. We hypothesised the haematological parameter combining traditional CBC parameters may improve the diagnostic efficacy for sCAP. Therefore, this retrospective study was designed to evaluate the diagnostic and prognostic values of a new haematological model for sCAP, and to compare the new model with other commonly used inflammatory markers. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3491/rc).

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Methods

Study design and patient groups

This study was approved by the Independent Ethics Committee (IEC) for Clinical Research and Animal Trials of The First Affiliated Hospital of Sun Yat-sen University [Approval No. (2021)827] and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was waived due to the retrospective nature of the study.

A total of 100 healthy subjects, 100 common pneumonia (CP) patients and 111 sCAP patients from our hospital were enrolled in the study between December 2020 and June 2021. The diagnostic gold standard of CP and sCAP referred to the *China Expert Consensus on Clinical Practice of Critical and Severe Pneumonia* (1) (Table S1 for detailed diagnostic criteria). CP was defined by the following criteria: Chest imaging shows new patchy infiltrative opacities or interstitial changes, with or without pleural effusion. And meets at least one of the following signs: (I) new cough or expectoration or aggravation of existing respiratory symptoms, with purulent sputum, with or without chest pain; (II) fever; (III) signs of pulmonary consolidation and/or wet rales; (IV) WBC >10×10^9/L or <4×10^9/L, with or without a left shift of the nucleus. sCAP was defined by the following criteria: meets at least one of the following criteria: (I) tracheal intubation and requiring mechanical ventilation; (II) vasoactive agents still required after aggressive fluid resuscitation for septic shock. Or meets three of the following criteria: (I) respiratory rate ≥30 breaths per minute; (II) PaO$_2$/FiO$_2$ (ratio of partial pressure of O$_2$ in arterial blood to fraction of inspired oxygen) ≤250 mmHg; (III) multilobar infiltration; (IV) confusion and/or disorientation; (V) blood urea nitrogen (BUN) ≥20 mg/dL; (VI) leukopenia (WBC <4×10^9/L); (VII) thrombocytopenia (PLT <100×10^9/L); (VIII) hypothermia (central body temperature <36 ℃); (IX) hypotension requiring fluid resuscitation. Subjects who had the following condition were excluded: (I) age younger than 18 years of age; (II) missing CBC, CRP, or PCT results; (III) haematological diseases, tumours or immunosuppressant use.

Data collection

Medical records were reviewed, and basic information, history of illnesses, clinical symptoms, and 28-day survival were recorded. A Mindray BC-6800 Plus automated haematology analyser (Mindray, Shenzhen, China) was used for CBC analysis to output CBC parameters and haematological parameters. Moreover, a Roche cobas E601 automated biochemical immunoassay analyser (Basel, Switzerland) was used to analyse serum samples collected at the same time to obtain serum CRP and PCT levels. All tests were completed within 6 hours of sample collection, and the investigators were blinded to the patient groups during information and data collection.

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages and analysed with chi-square test or Fisher's exact test. Continuous variables were analysed with the Kolmogorov-Smirnov test for normality. Normally distributed data were expressed as the mean and standard deviation (SD) and analysed with analysis of variance (ANOVA) for multigroup comparisons then the Turkey-Kramer test for pairwise comparisons. Nonnormally distributed data were expressed as the median and interquartile range (IQR) and analysed with Kruskal-Wallis nonparametric test for multigroup comparisons then Dunn's test for pairwise comparisons.

With the sCAP group as the positive group and the CP group as the negative group, logistic regression was used to establish a new haematological model combining WBC and haematological parameter.

To evaluate the clinical value of the new haematological model, CRP, and PCT in patients with sCAP, we built a receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC), with the sCAP group as the positive group and the CP group as the negative group. An optimal threshold based on the Youden index (Youden index = sensitivity + specificity − 1) and the clinical settings was selected to compare the sensitivity and specificity of these parameters.

A two-dimensional scatter plot was drawn with the value of new model as the Y-axis and CRP or PCT as the X-axis to evaluate the relationship between the new model and CRP or PCT.

Pneumonia patients were divided into a survival group and a death group based on their 28-day survival. ROC curve analysis was performed to compared the values of WBC & Mon-XW, CRP and PCT between the two groups. Survival prognosis for sCAP were evaluated by univariate and multivariate logistic regression. In additions, 28-day survival curves were plotted to evaluate the prognostic value of the new model.

Table 1 Characteristics of pneumonia patients

Variables	Total (N=211)	CP (n=100)	sCAP (n=111)	P
Age (years)	65.3±16.0	65.6±16.4	65.1±15.7	0.758
Male	145 (68.7)	61 (61.0)	84 (75.7)	<0.050
History of hypertension	90 (42.7)	45 (45.0)	45 (40.5)	0.513
History of diabetes	46 (21.8)	20 (20.0)	26 (23.4)	0.548
History of smoking	62 (29.4)	25 (25.0)	37 (33.3)	0.185
History of stroke	18 (8.5)	10 (10.0)	8 (7.2)	0.468
History of cardiovascular disease	22 (10.4)	12 (12.0)	10 (9.0)	0.478
Cough	107 (50.7)	55 (55.0)	52 (46.8)	0.237
Expectoration	100 (47.4)	53 (53.0)	47 (42.3)	0.121
Fever	97 (46.0)	42 (42.0)	55 (49.5)	0.272
Shortness of breath	92 (44.7)	42 (42.0)	50 (46.7)	0.535
Difficulty breathing	71 (33.6)	11 (11.0)	60 (54.1)	<0.001
Palpitations	16 (7.6)	9 (9.0)	7 (6.3)	0.461
Chest tightness	58 (27.5)	30 (30.0)	28 (25.2)	0.438
Pulmonary rales	113 (53.5)	39 (39.0)	74 (66.7)	<0.001
Oedema	39 (18.5)	19 (19.0)	20 (18.0)	0.854
Temperature (℃)	37.2±1.1	37.1±1.0	37.3±1.1	0.297
Diastolic blood pressure (mmHg)	87.8±32.5	93.1±34.6	83.1±2.8	<0.050
Systolic blood pressure (mmHg)	113.9±31.1	119.9±31.3	108.5±30.0	<0.010
Heart rate (bpm)	94.5±19.5	89.6±16.2	99.0±21.1	<0.010
Respiratory rate (breaths per minute)	21.4±6.2	19.8±2.7	22.8±7.9	<0.010

Data are represented as mean ± SD or number (%). CP, common pneumonia; sCAP, severe community-acquired pneumonia; SD, standard deviation.

SPSS (version 21.0, SPSS Inc., Chicago IL, USA) was used for data statistics, and GraphPad Prism (version 8.0, GraphPad Software, San Diego CA, USA) was used for graphing. All tests were two-sided, and P<0.05 was considered statistically significant.

Results

Characteristics of pneumonia patients

A total of 211 pneumonia patients were included in this study, including 100 patients (47.4%) in the CP group and 111 patients (52.6%) in the sCAP group (*Table 1*). The median age was 65.3 years, the proportion of male subjects was higher in the sCAP group (75.7%) than in the CP group (61.0%), 54.1% of patients in the sCAP group had

difficulty breathing compared with 11.0% in the CP group (P<0.001), and 66.7% of sCAP patients had pulmonary rales, which was significantly higher than that in the CP group (39.0%, P<0.001).

Haematological parameters for the diagnosis of sCAP

Table 2 shows all haematological parameters were higher in the two pneumonia groups than in the control group, and all parameters but Mon# (absolute monocyte count) were significantly higher in the sCAP group than in the CP group (P<0.05). Moreover, all parameters but Mon# increased from group 1 to group 3 (*Figure 1*), and this trend was most pronounced for Mon-XW (P<0.0001 from group 1 to group 2, and from group 2 to group 3).

Table 2 Comparison of parameters among the three groups

Parameter	Group 1 (n=100)	Group 2 (n=100)	Group 3 (n=111)	P
WBC	6.3 (5.2, 7.1)[a]	9.9 (7.4, 13.0)[a]	12.2 (8.4, 18.5)[a]	<0.0001
Neu#	3.4 (2.9, 4.2)[a]	8.0 (5.1, 10.8)[a]	10.2 (6.9, 16.4)[a]	<0.0001
Mon#	0.4 (0.3, 0.5)[b]	0.6 (0.45, 0.92)[c]	0.6 (0.27, 0.94)[d]	<0.0001
Neu-X	324.8 (311.4, 342.8)[a]	356.5 (333.5, 377.7)[e]	368.5 (339.9, 396.4)[e]	<0.0001
Neu-XW	227.6 (214.6, 242.7)[a]	252.6 (235.2, 284.6)[e]	271.1 (246.3, 307.1)[e]	<0.0001
Neu-Y	405.5 (392.2, 419.6)[a]	447.8 (425.3, 469.7)[a]	473.7 (443.9, 521.5)[a]	<0.0001
Neu-YW	176.7 (170.6, 183.8)[a]	201.6 (190.2, 211.9)[a]	216.3 (201.2, 258.8)[a]	<0.0001
Mon-X	187.3 (180.5, 191.5)[a]	209.4 (200.8, 216.2)[a]	217.5 (208.4, 228.5)[a]	<0.0001
Mon-XW	68.5 (66.1, 72.2)[a]	80.4 (74.7, 85.9)[a]	91.1 (84.0, 103.6)[a]	<0.0001
Mon-Y	902.7 (872.5, 925.6)[a]	946.2 (901.2, 980.5)[e]	961.9 (903.2, 1,019.1)[e]	<0.0001
Mon-YW	342.8 (321.2, 358.3)[a]	403.8 (379.6, 441.0)[a]	454.2 (413.3, 509.1)[a]	<0.0001

[a], a very significant statistical difference versus other groups (P<0.0001); [b], a significant statistical difference versus the CP group (P<0.01) and a very significant statistical difference versus the sCAP group (P<0.0001); [c], a very significant statistical difference versus the control group (P<0.01) but no difference versus the sCAP group (P>0.05); [d], a very significant statistical difference versus the control group (P<0.01) but no difference versus the CP group (P>0.05); [e], a very significant statistical difference versus other groups (P<0.01). WBC, white blood cell count; Neu#, absolute neutrophil count; Mon#, absolute monocyte count; Neu-X, neutrophils cell complexity; Neu-XW, neutrophils complexity distribution width; Neu-Y, neutrophils fluorescence intensity; Neu-YW, neutrophils fluorescence intensity distribution width; Mon-X, monocytes cells complexity; Mon-XW, monocytes complexity distribution width; Mon-Y, monocytes fluorescence intensity; Mon-YW, monocytes fluorescence intensity distribution width; CP, common pneumonia; sCAP, severe community-acquired pneumonia.

ROC analysis was performed to evaluate the diagnostic efficacy of these haematological parameters for sCAP, with a higher AUC value indicating better diagnostic efficacy. The optimal threshold was selected based on the Youden index (Youden index = sensitivity + specificity – 1) and the clinical settings. *Table 3* shows the AUCs (sensitivity, specificity) were 0.637 (64%, 60%) for WBC and 0.651 (56.8%, 68%) for Neu# (absolute neutrophil count), both of which are common haematology infection parameters. The diagnostic efficacies of Mon# [0.569 (40.5%, 82.0%)], Neu-X [0.596 (54.1%, 67.0%)], Neu-XW [0.621 (64.0%, 60.0%)], and Mon-Y [0.569 (43.2%, 76.0%)] were weaker than those of WBC and Neu#, while the diagnostic efficacies of Neu-Y [0.688 (54.1%, 77.0%)], Neu-YW [0.714 (62.2%, 75.0%)], Mon-XW [0.792 (64.9%, 81.0%)], and Mon-YW [0.736 (81.1%, 56.0%)] were higher than that of WBC and Neu#. Mon-XW had the highest AUC value of 0.792 (64.9%, 81%), indicating the best diagnostic efficacy for sCAP. Based on this result, we combined Mon-XW and the common infection parameter WBC to establish a new

haematological model to improve diagnostic efficacy.

Composition of the new haematological model

Figure 2 shows the distribution of WBC and Mon-XW in the two-dimensional scatter plot, vividly demonstrating the effect of combining the two parameters. Samples from the control group are mainly distributed in the lower left area, those from the sCAP group are mainly distributed in the upper right area, and those from the CP group are somewhere in between. The combination of WBC and Mon-XW could separate the three groups, indicating good discrimination.

Logistic regression was performed to build the new haematological model WBC & Mon-XW with WBC and Mon-XW (*Table 4*). Omnibus tests confirmed the statistical significance of the logistic model (P<0.001) as well as both independent variables (WBC and Mon-XW) (P<0.0001). Each 1-unit increase in WBC was associated with a 9.8% [odds ratio (OR) =1.098, 1.042–1.157] increase in the risk
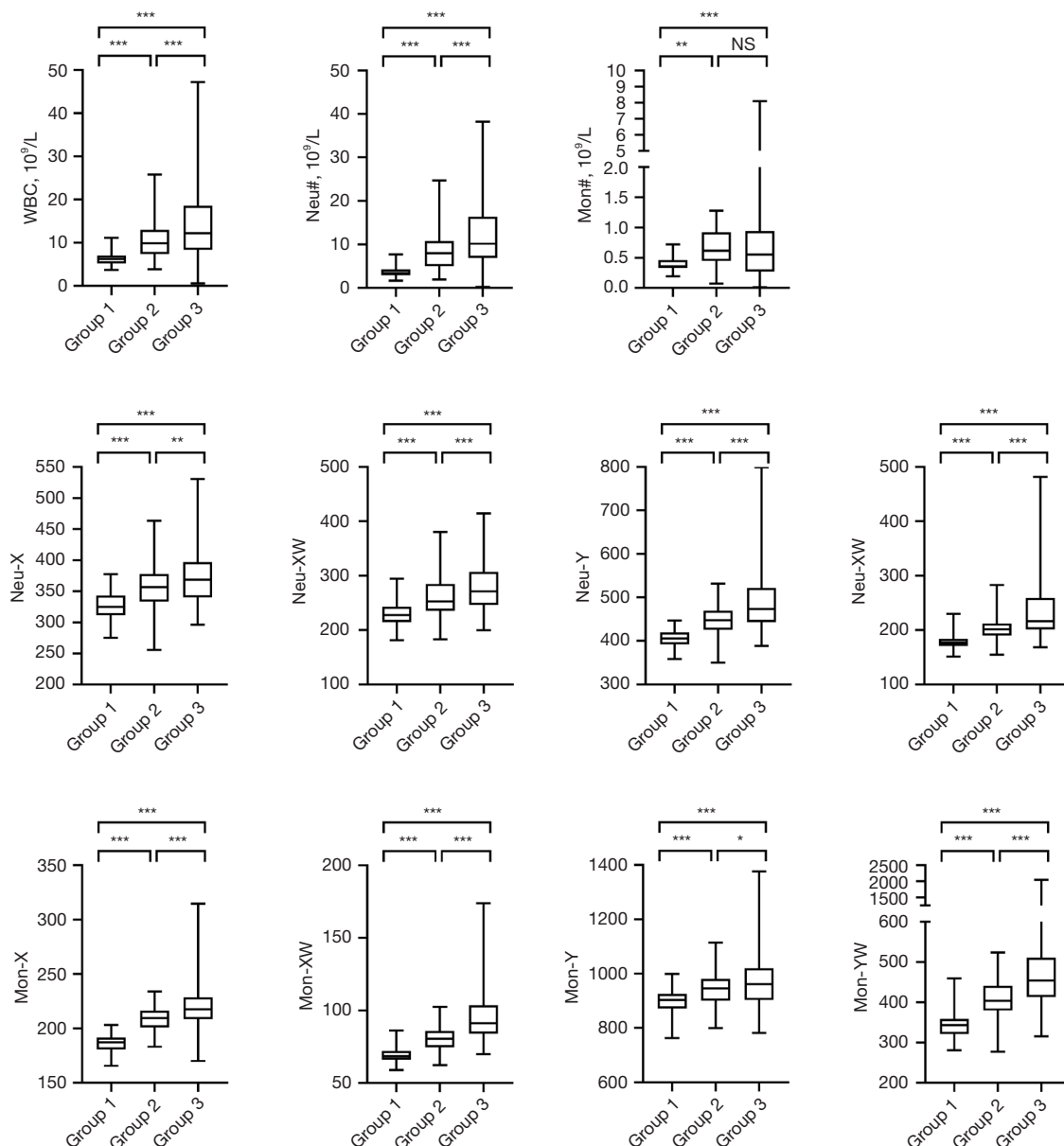
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Figure 1 Boxplot comparison of each parameter among the three groups. *, a statistical difference, P<0.05; **, a significant statistical difference, P<0.01; ***, a very significant statistical difference, P<0.0001. NS, no statistical difference; WBC, white blood cell count; Neu#, absolute neutrophil count; Mon#, absolute monocyte count; Neu-X, neutrophils cell complexity; Neu-XW, neutrophils complexity distribution width; Neu-Y, neutrophils fluorescence intensity; Neu-YW, neutrophils fluorescence intensity distribution width; Mon-X, monocytes cells complexity; Mon-XW, monocytes complexity distribution width; Mon-Y, monocytes fluorescence intensity; Mon-YW, monocytes fluorescence intensity distribution width.

Table 3 ROC curve results of each parameter

Parameter	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
WBC	0.637	0.562–0.712	10.6	64.0	60.0
Neu#	0.651	0.578–0.725	9.6	56.8	68.0
Mon#	0.569	0.491–0.648	0.4	40.5	82.0
Neu-X	0.596	0.519–0.672	366.9	54.1	67.0
Neu-XW	0.621	0.546–0.697	260.4	64.0	60.0
Neu-Y	0.688	0.618–0.759	470.5	54.1	77.0
Neu-YW	0.714	0.645–0.783	211.2	62.2	75.0
Mon-X	0.694	0.624–0.765	216.5	54.1	78.0
Mon-XW	0.792	0.733–0.851	86.6	64.9	81.0
Mon-Y	0.569	0.491–0.647	980.6	43.2	76.0
Mon-YW	0.736	0.669–0.802	407.8	81.1	56.0

ROC, receiver operator characteristic; AUC, area under the curve; CI, confidence interval; WBC, white blood cell count; Neu#, absolute neutrophil count; Mon#, absolute monocyte count; Neu-X, neutrophils cell complexity; Neu-XW, neutrophils complexity distribution width; Neu-Y, neutrophils fluorescence intensity; Neu-YW, neutrophils fluorescence intensity distribution width; Mon-X, monocytes cells complexity; Mon-XW, monocytes complexity distribution width; Mon-Y, monocytes fluorescence intensity; Mon-YW, monocytes fluorescence intensity distribution width; CI, confidence interval.
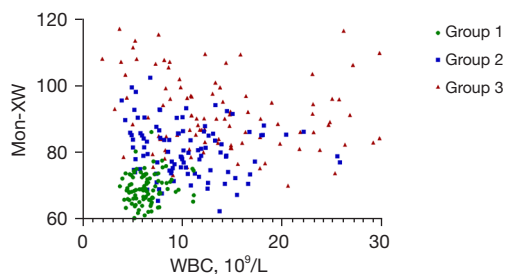

Figure 2 WBC and Mon-XW two-dimensional scatter plot. WBC, white blood cell count; Mon-XW, monocytes complexity distribution width.

of progression to sCAP, and for Mon-XW, the number was 9.2% (OR =1.092, 1.059–1.126).

New haematological model, CRP, and PCT as diagnostic indicators for sCAP

In *Figure 3* and *Table 5*, WBC & Mon-XW and CRP were significantly different among and between the three groups (P<0.01), with an increase from group 1 to group 3. PCT was highest in the sCAP group (P<0.05), with no significant difference between the control group and the CP group (P>0.05).

Furthermore, ROC analysis was performed to evaluate the diagnostic efficacy of WBC & Mon-XW, CRP, and PCT for sCAP. The AUC of WBC & Mon-XW was 0.842, and at the cut-off value of 8.47, the sensitivity was 80.2%, and the specificity was 71.0%, which were superior to those of WBC or Mon-XW alone (*Figure 4*). The AUCs (sensitivity, specificity) for CRP and PCT, two common inflammation indicators, were 0.633 (73.9%, 52%) and 0.750 (72.1%, 63%), respectively, indicating good yet inferior diagnostic efficacy to WBC & Mon-XW (*Table 6*). *Figure 5* demonstrates significant positive correlations between the new haematological model and the common inflammation markers CRP and PCT.

The new haematological model for the prognostic evaluation of pneumonia patients

ROC analysis was performed to evaluate the survival prognostic performance of WBC & Mon-XW, CRP, and PCT. The AUC of WBC & Mon-XW was 0.748, higher than that of CRP and PCT (*Figure 6*). When WBC & Mon-XW cut-off value was 8.9, sensitivity and specificity were 71.4% and 70.9 respectively (*Table 7*).

At the univariate logistic regression analysis, age (P=0.01), diastolic blood pressure (P0.003), systolic blood pressure

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Table 4 Binary logistic regression for sCAP

Parameter	Regression coefficient B	SE	Wals	df	P	OR	95% CI
WBC	0.093	0.027	12.155	1	0.000	1.098	1.042–1.157
Mon-XW	0.088	0.016	31.561	1	0.000	1.092	1.059–1.126
Constant	−8.871	1.459	36.951	1	0.000	0.000	–

sCAP, severe community-acquired pneumonia; SE, standard error; df, degrees of freedom; OR, odds ratio; CI, confidence interval; WBC, white blood cell count; Mon-XW, monocytes complexity distribution width.
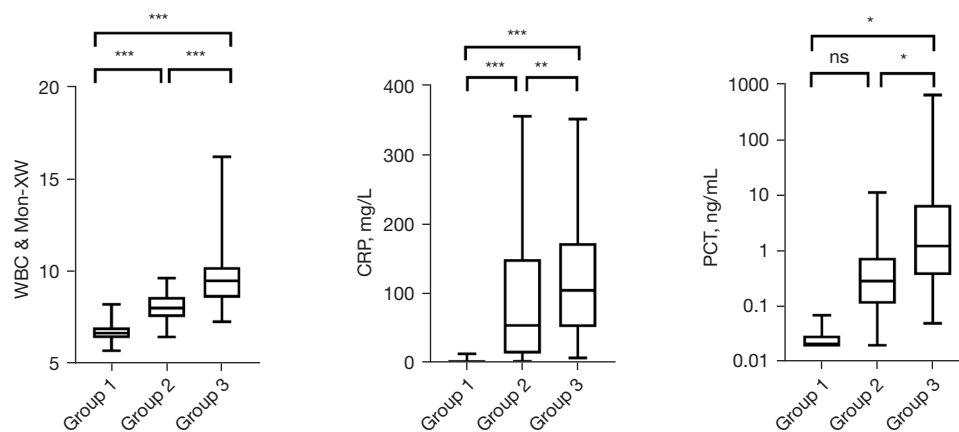
Figure 3 Boxplots of the new haematological model, CRP, and PCT. *, a statistical difference, P<0.05; **, a significant statistical difference, P<0.01; ***, a very significant statistical difference, P<0.001. ns, no statistical difference; WBC, white blood cell count; Mon-XW, monocytes complexity distribution width; CRP, C-reactive protein; PCT, procalcitonin.

Table 5 Comparison of parameters among the three groups

Parameter	Group 1 (n=100)	Group 2 (n=100)	Group 3 (n=111)	P
WBC & Mon-XW	6.65 (6.39, 6.97)[a]	8.02 (7.53, 8.62)[a]	9.50 (8.58, 10.24)[a]	<0.0001
CRP	0.66 (0.29, 1.52)[a]	54.37 (14.00, 150.21)[b]	150.21 (52.63, 172.61)[b]	<0.0001
PCT	0.02 (0.02, 0.03)[c]	0.29 (0.11, 0.76)[d]	1.24 (0.37, 6.81)[e]	<0.0001

[a], a very significant statistical difference versus other groups (P<0.0001); [b], a significant statistical difference versus other groups (P<0.01); [c], no statistical difference versus the CP group (P>0.05) and a statistical difference versus the sCAP group (P<0.05); [d], no statistical difference versus the control group (P>0.05) and a statistical difference versus the sCAP group (P<0.05); [e], a statistical difference versus other groups (P<0.05). WBC, white blood cell count; Mon-XW, monocytes complexity distribution width; CRP, C-reactive protein; PCT, procalcitonin; CP, common pneumonia; sCAP, severe community-acquired pneumonia.

(P<0.001) and WBC & Mon-XW (P=0.002) were found associated with the death of pneumonia. However, at the multivariate analysis age (P=0.001), gender (P=0.04), history of smoking (P=0.046), blood pressure (P<0.001), heart rate (P=0.034) and WBC & Mon-XW (P<0.001) were the independent predictors for the death of pneumonia. The OR values of history of smoking (OR =2.74) and WBC & Mon-XW (OR =1.82) were higher than those of other

variables (*Table 8*).

We followed and recorded the 28-day survival data of 162 pneumonia patients after diagnosis. Patients were divided into the WBC & Mon-XW <8.9 (n=81) group and the WBC & Mon-XW ≥8.9 (n=81) group based on WBC & Mon-XW on the day of diagnosis. Twenty-eight-day survival curves were plotted to observe the relationship between patient survival and the new haematological model. By day
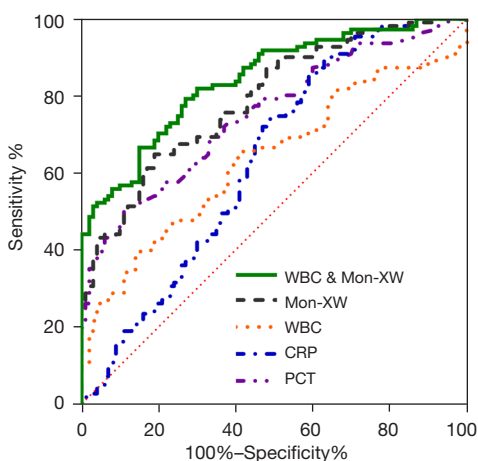
Figure 4 ROC curve results of each parameter for sCAP. WBC, white blood cell count; Mon-XW, monocytes complexity distribution width; CRP, C-reactive protein; PCT, procalcitonin; ROC, receiver operator characteristic; sCAP, severe community-acquired pneumonia.

28 after diagnosis, 28 of 162 patients (17.3%) died, 20 of whom (71.4%) were in the WBC & Mon-XW ≥8.9 group. *Figure* 7 shows the 28-day mortality rate was approximately 40% in the WBC & Mon-XW ≥8.9 group, which is approximately 15% higher than that in the WBC & Mon-XW <8.9 group.

Discussion

sCAP is a common critical infectious disease in clinical practice. Patients often suffer from severe disease, progress rapidly, and develop respiratory failure in a short period, and in most cases, simple pulmonary infection rapidly progresses to systemic infection. In addition to pulmonary symptoms, patients often present with sepsis, septic shock, coagulation abnormalities, and multiple organ insufficiency or even failure, with an extremely high mortality rate. Early, rapid, and accurate diagnosis is critical for treatment,

Table 6 ROC curve results of each parameter for sCAP

Parameter	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
WBC	0.637	0.562–0.712	10.6	64.0	60.0
Mon-XW	0.792	0.733–0.851	86.6	64.9	81.0
WBC & Mon-XW	0.842	0.791–0.894	8.47	80.2	71.0
CRP	0.633	0.557–0.710	55.2	73.9	52.0
PCT	0.750	0.685–0.815	0.5	72.1	63.0

ROC, receiver operator characteristic; sCAP, severe community-acquired pneumonia; AUC, area under the curve; CI, confidence interval; WBC, white blood cell count; Mon-XW, monocytes complexity distribution width; CRP, C-reactive protein; PCT, procalcitonin.
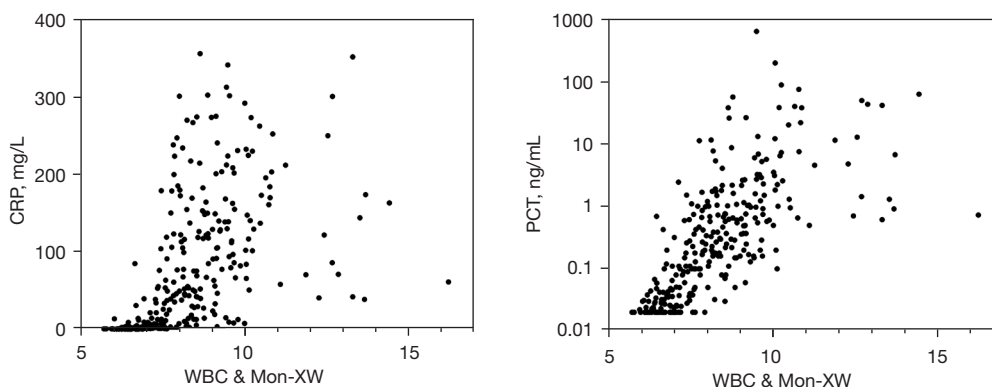

Figure 5 Two-dimensional correlation plots of the new haematological model and CRP or PCT. Significant positive correlations are seen between the new model and the common inflammation markers CRP and PCT. CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; Mon-XW, monocytes complexity distribution width.

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optimal survival, and prognosis. WBC assessment represents an important indicator for clinical judgement of bacterial infection, but its sensitivity and specificity are not yet adequately high. While other auxiliary indicators such as CRP, PCT, and IL-6 are widely used in clinical practice, they have limitations in timeliness and diagnostic efficacy, and cannot meet the needs of clinical diagnosis. Therefore, developing a rapid, effective, accurate, and cost-effective test for sCAP is important.

During bacterial infection, monocytes are activated and play bactericidal and phagocytic roles to defend against pathogenic microorganisms. They play a central role in the immune response against microorganisms and
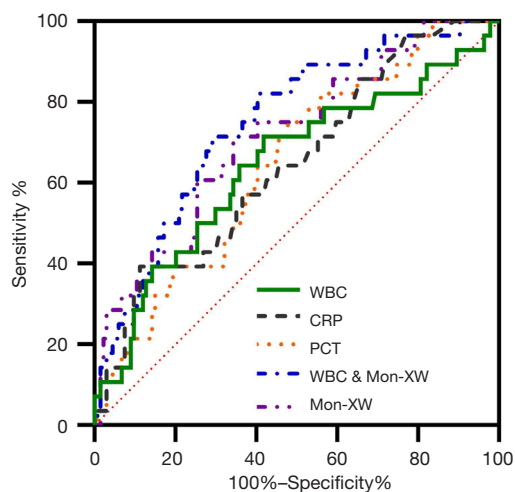
Figure 6 ROC curve analysis for the 28-days mortality of sCAP. WBC, white blood cell count; CRP, C-reactive protein; PCT, procalcitonin; Mon-XW, monocytes complexity distribution width; ROC, receiver operator characteristic; sCAP, severe community-acquired pneumonia.

the mechanism of acute infection. As a first-line defence against infection, in addition to phagocytising and killing microorganisms and producing cytokines, monocytes present microbial antigens to T cells, initiating and regulating cellular and humoral immunity. Monocytes activated to play bactericidal roles undergo morphological changes, becoming morphologically different from normal monocytes. This morphological change is a more direct indicator of the body's stress response and defence mechanism against bacterial invasion and may be used as an accurate auxiliary diagnostic indicator of sCAP. In recent years, haematology analysers have progressed rapidly due to technological advancements. Mindray's next-generation haematology analyser BC-6800 Plus uses cutting-edge SF-Cube technology for rapid testing of several blood cells and outputs a range of new haematological parameters, which accurately reflect morphological changes in monocytes, indirectly reflecting the infection status of patients.

This study shows Mon-XW has a good diagnostic value for sCAP, with an AUC of 0.792. Its diagnostic efficacy is optimal at a cut-off value of 86.6, and its sensitivity and specificity are 64.9% and 81%, respectively. Therefore, we performed binary logistic regression to linearly combine Mon-XW and WBC to evaluate the value of this new model for sCAP, and the results show it was significantly higher in the sCAP group than in the control group and the CP group ($P<0.0001$), with a significant difference between the two groups ($P<0.0001$). Moreover, CRP and PCT were higher in the sCAP group than in the control group ($P<0.05$). These data indicate the new parameter, CRP, and PCT can be used as auxiliary diagnostic indicators for sCAP and as differential diagnostic indicators between sCAP and CP.

Several studies have shown monocyte haematological

Table 7 ROC curve results of each parameter for the death of pneumonia patients

Parameter	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
WBC	0.644	0.522–0.767	10.84	71.4	58.2
Mon-XW	0.713	0.607–0.819	86.1	71.4	65.7
WBC & Mon-XW	0.748	0.651–0.845	8.9	71.4	70.9
CRP	0.647	0.540–0.753	70.5	75.0	52.2
PCT	0.647	0.535–0.758	2.6	39.3	88.8

ROC, receiver operator characteristic; AUC, area under curves; CI, confidence interval; WBC, white blood cell count; Mon-XW, monocytes complexity distribution width; CRP, C-reactive protein; PCT, procalcitonin.

Table 8 Baseline characteristics in pneumonia patients and the multivariate model of death risk by COX regression

Variables	Survivors (N=134)	Non-survivors (N=28)	Univariate	Multivariate	
			P	OR (95% CI)	P
Age (years)	64.1±16.9	72.4±14.7	0.010	1.05 (1.02–1.08)	0.001
Male	87 (64.9)	20 (71.4)	0.098	0.34 (0.13–0.95)	0.040
History of hypertension	57 (42.5)	14 (50.0)	0.306		
History of diabetes	29 (21.6)	11 (39.3)	0.145		
History of smoking	44 (32.8)	7 (25.0)	0.113	2.74 (1.02–7.37)	0.046
History of stroke	10 (7.5)	4 (14.3)	0.457		
Expectoration	68 (50.7)	12 (42.9)	0.939		
Fever	57 (42.5)	15 (53.4)	0.685		
Shortness of breath	57 (43.2)	12 (46.2)	0.573		
Difficulty breathing	35 (26.1)	13 (46.4)	0.771		
Chest tightness	38 (28.4)	5 (17.9)	0.627		
Pulmonary rales	65 (48.5)	17 (60.7)	0.068		
Oedema	29 (21.6)	4 (14.2)	0.093		
Temperature (℃)	37.2±1.0	37.2±1.42	0.624		
Diastolic blood pressure (mmHg)	91.8±33.1	82.8±33.9	0.003	0.96 (0.95–0.98)	0.000
Systolic blood pressure (mmHg)	119.0±30.9	97.9±30.8	0.000	0.95 (0.94–0.97)	0.000
Heart rate (bpm)	92.0±16.4	100.9±24.1	0.068	1.02 (1.01–1.04)	0.034
Respiratory rate (breaths per minute)	20.9±5.0	23.5±7.2	0.887		
CRP	96.3±83.7	138.8±93.3	0.732		
PCT	4.7±21.0	29.8±123.8	0.354		
WBC & Mon-XW	8.5±1.3	9.7±1.6	0.002	1.82 (1.32–2.52)	0.000

Data are represented as mean ± SD or number (%). OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; Mon-XW, monocytes complexity distribution width.
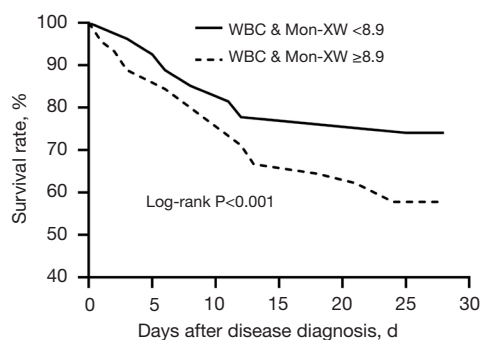

Figure 7 The 28-day survival curves of pneumonia patients. WBC, white blood cell count; Mon-XW, monocytes complexity distribution width.

parameters may be indicative of sepsis. Crouser et al. argued that during pathogen invasion, monocytes are activated to fight pathogens, resulting in a rapid increase in their volume. The monocyte distribution width (MDW) reflects this volume change and can be used as an auxiliary diagnostic indicator for sepsis (20). At the threshold of 20.5, its sensitivity is 77%, and specificity is 73%, and combining with WBC further improves diagnostic efficacy, with an ROC-AUC of 0.89. Buoro et al. investigated the correlations between both the neutrophil fluorescence intensity (NE-SFL) and monocyte internal structure (MO-X) with disease severity and found they were most effective in diagnosing sepsis in all patients (AUCs: 0.75,

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0.72, respectively). These parameters were also significantly correlated with the SOFA score, suggesting they may provide useful information for the management of sepsis patients (25). Urrechaga *et al.* also investigated MO-X in sepsis cases (26), and found that at a threshold of 118.8, its sensitivity, specificity, positive predictive value, and negative predictive value were 78.3%, 84.9%, 58.4%, and 93.5%, respectively, effectively facilitating the diagnosis. Taken together, these data demonstrate the value of haematological parameters in infectious disease.

In addition to good diagnostic efficacy, the new haematological parameter has the following advantages. Firstly, CBC is considered a routine test for daily management and monitoring of patients, and as the new parameter is derived from CBC, no additional samples or costs are required. Secondly, CBC can be completed in five minutes, allowing clinicians to quickly determine the infection status of patients. Thirdly, the haematology analyser is easy to operate and suitable for emergencies at any time of day, and finally, as a quantitative parameter, the new parameter is more objective than manual microscopic observation of morphological changes and the result is more reliable because thousands of cells can be tested at the same time.

This study has some limitations. First, this is a retrospective study, and the level of evidence is relatively low, and multicentre prospective cohort studies are warranted in the future. Second, the new parameter is related to the morphology of blood cells, and the conclusion would be more objective if the results were compared with microscopic observations of standard blood smears. Third, further analysis of the effect of the new parameter on clinical decisions, such as ICU stay and medications, is required.

In short, this study shows the new parameter combining WBC and Mon-XW reflects the infection responses of and morphological changes in neutrophils and monocytes. It can be used for auxiliary diagnosis and prognostic evaluations of sCAP, and has superior diagnostic efficacy compared to CRP and PCT.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the IEC for Clinical Research and Animal Trials of The First Affiliated Hospital of Sun Yat-sen University [Approval No. (2021)827]. Informed consent was waived due to the retrospective nature of the study.

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Table S1 Diagnostic criteria for CP and sCAP

Common pneumonia	Severe community-acquired pneumonia
Any of items 1–4 plus item 5: ① New cough or expectoration or aggravation of existing respiratory symptoms, with purulent sputum, with or without chest pain; ② Fever; ③ Signs of pulmonary consolidation and/or wet rales ④ WBC >10×10^9/L or <4×10^9/L, with or without a left shift of the nucleus; ⑤ Chest imaging showing new patchy infiltrative opacities or interstitial changes, with or without pleural effusion And excluding tuberculosis, lung tumour, non-infectious pulmonary interstitial disease, pulmonary oedema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis	Any of the primary criteria or ≥3 secondary criteria Primary criteria: ① Tracheal intubation and requiring mechanical ventilation; ② Vasoactive agents still required after aggressive fluid resuscitation for septic shock Secondary criteria: ① Respiratory rate ≥30 breaths per minute; ② PaO$_2$/FiO$_2$ ≤250 mmHg; ③ Multilobar infiltration; ④ Confusion and/or disorientation; ⑤ BUN ≥20 mg/dL; ⑥ Leukopenia (WBC <4×10^9/L); ⑦ Thrombocytopenia (PLT <100×10^9/L); ⑧ Hypothermia (central body temperature <36 ℃); ⑨ Hypotension requiring fluid resuscitation

CP, common pneumonia; sCAP, severe community-acquired pneumonia; WBC, white blood cells count; PaO$_2$/FiO$_2$, ratio of partial pressure of O$_2$ in arterial blood to fraction of inspired oxygen; BUN, blood urea nitrogen; Plt, platelet.