Procalcitonin and C-reactive Protein Perform Better Than Neutrophil-Lymphocyte Count Ratio on Evaluation of Hospital Acquired Pneumonia

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Research article

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Abstract

Background: The relationship between biomarkers and hospital acquired pneumonia (HAP) is under studied, especially those severe cases admitted to the intensive care unit (ICU). Compared with community acquired pneumonia (CAP), HAP might have different traits regarding biomarkers due to the previous history in the hospitals.

Methods: 593 adult patients were enrolled into this retrospective cohort study to determine neutrophil-lymphocyte count ratio (NLCR), procalcitonin (PCT), C-reactive protein (CRP) and serum lactate level at the admission of ICU. According to the diagnosis, patients were divided into two groups: non-infection and HAP. Discriminant analysis was performed based on better outcomes of diagnostic performance and severity evaluation. The diagnostic performance of each individual biomarker was assessed by construction of receiver operating characteristic (ROC) curves and calculation of the area under each ROC curves (AUROC). Multivariable analysis was also applied to determine most appropriate prognostic factors.

Results: NLCR, PCT and CRP between non-infection and HAP group showed remarkable differences. Because of discriminant ability of severe infection, the AUROC of NLCR (0.626; 95%CI 0.581-0.671) was not comparative with conventional markers such as CRP (0.685; 95% CI 0.641-0.730) and PCT (0.661; 95% CI 0.615-0.707). Besides, AUROC of composite biomarkers, especially the combination of NLCR, CRP and WBC, were significantly greater than the single biomarkers.

Conclusions: NLCR was not comparable to conventional single biomarkers such as CRP and PCT regarding to diagnosis or severity evaluation of HAP. Composite biomarkers could prompt early diagnosis and severity evaluation with improved accessibility, especially the combination of NLCR, CRP and WBC.

Background

Hospital-acquired pneumonia (HAP) is characterized by pneumonia acquired during hospitalization in patients with or without invasive mechanical ventilation. HAP is a frequent incident for critical patients and remains the leading cause of death among hospital-acquired infections [1]. This life-threatening condition in intensive care unit (ICU) may require mechanical ventilation, associated with prolonged hospital stay and high mortality. Certain clinical and laboratory parameters were applied to facilitate diagnosis, evaluate severity, guide antibiotic administration and predict prognosis of HAP. However, most of them has been proved to be not effective enough on its severity evaluation and outcome prediction.

Procalcitonin (PCT) is a useful serum marker in prediction, diagnosis and severity evaluation of bacterial infections in critically ill patients [2]. It has been shown to be associated with the severity of inflammation and prognosis during sepsis and septic shock [3,4]. Some large studies have demonstrated that increased levels of PCT was associated with bacterial aetiology of community acquired pneumonia (CAP) and

adverse short-term outcome [5]. The significance of PCT has been emphasized that different level patterns may be useful to guide antimicrobial therapy in patients with various infections, such as community acquired lower respiratory tract infection[6], ventilation acquired pneumonia [7], blood stream infection [8] and abdominal infection [9].

C-reactive protein (CRP), a highly conserved plasma protein, is a homopentameric acute-phase inflammatory protein, which was initially discovered in 1930 by Tillet and Francis. CRP exhibits elevated expression during inflammatory conditions such as rheumatoid arthritis, cardiovascular disease and infection. As an acute phase protein, the plasma concentration of CRP deviates by at least 25% during inflammatory disorders [10]. CRP, as a conventional biomarker, also plays great role at identifying and evaluating bacterial infections [11]. Although been proved to be predictive on severity of pneumonia, only very few poor quality investigations compared its potential with NLCR for evaluation of inflammation [12].

Numerous studies have evaluated diagnostic and evaluative performance of neutrophil lymphocyte count ration (NLCR) on various clinical conditions such as sepsis [13], septic shock [14], bacteremia [15,16], renal, lung and colorectal carcinomas and intracranial tumors [17]. Besides, NLCR has been proved to be able to predict severity and outcome of CAP with higher prognostic accuracy as compared with traditional infection markers in the emergency department [12].

Composite biomarkers have been applied to evaluate respiratory tract infection, however few studies have focused on their diagnostic accuracy and prognostic utility. Some findings showed greater value for composite biomarkers in discriminating severity of inflammation [18,19,20]. In this study, we intended to compare the diagnostic performance of composite biomarkers with single biomarkers.

As mentioned above, different biomarkers have been applied to evaluate severity of inflammation. With respect to the diagnostic accuracy and predictive potency, divergence of opinion has been largely presented. Currently, it is still controversial that NLCR may be less suitable to detect the presence of sepsis in ICU patients [13]. Moreover, data about the comparison of NLCR and conventional markers in patients with HAP are very limited. Thus, this study was to clarify whether NLCR presents advantages over conventional markers, or whether composite biomarkers could be a better choice for diagnosis and evaluation of HAP.

Methods

Patients and study design

This retrospective study was conducted with data collected from Jan 2017 to June 2019 at the First Affiliated Hospital of Nanjing Medical University, a tertiary hospital with more than 2000 beds, in the southeast region of China. Patients admitted to the ICU in suspicion of HAP or non-infection were consecutively enrolled into this study. Patients with other infection, such as infection of cholecyst, skin and soft tissue, urinary system, abdomen or central nervous system were all excluded. All the physiological and pathophysiological data, laboratory and microbiological results were recorded accordingly. For microbiological analysis, culture findings were based upon both airway samples and blood culture. PCR (polymerase chain reaction) and EIA (enzyme immunoassay) based methods were involved for virus and antibody detection. Outcome in this study referred to 28-day survival, which was recorded according to both hospital mortality and proper followups.

Each medical record was subjectively reviewed by two senior specialists in ID respectively. According to HAP definition, these two independent specialists in infectious disease / critical care medicine followed the standard principle to recruit the cohort. Uncertainties were ruled out according to clinical symptoms, blood test, microbiological test and radiographic imaging.

HAP was defined in patients who developed pneumonia after 48 h of hospitalization when not receiving invasive mechanical ventilation (iMV) [21,22]. We recruited HAP patients at admission. Some of the patients required mechanical ventilation or non-invasive ventilatory support after admission. Clinical diagnosis of pneumonia was based on clinical criteria as suggested in the guidelines [21,23,24]: (1) new or progressive radiologic pulmonary infiltrate, (2) together with at least two of the following: temperature > 38 °C or < 36 °C, leukocytosis > 12,000/mm3 or leukopenia < 4000/mm3, or purulent respiratory secretions.

Inclusion criteria of the patients: (1) Adults: age of 18 to 89 years old; (2) Admitted to ICU in the First Affiliated Hospital of Nanjing Medical University during the period from Jan 2017 to Jun 2019; (3) Diagnosed with HAP or non-infectious disease.

Exclusion criteria of the patients: (1) Hematological disease; (2) Chemotherapy; (3) Receiving glucocorticoids; (4) Receiving bone marrow stimulators.

Enrolled patients were designated into two groups according to the diagnosis: (1) non-infection group: patients have been ruled out of infection of any origin and organism.; (2) HAP group: patients have been assessed as applicable to the criteria of HAP.

Statistical analysis

All continuous variables were expressed as the median and interquartile range due to non-normal distribution. F test was used to compare variances of continuous variables between two groups, if variances were significantly different, unpaired t test with Welch's correction would be applied. In the case of variances being equal, Mann-Whitney U test would be applied. $p < 0.05$ was considered the difference to be significant.

Composite biomarkers were constructed using bivariate logistic regression analysis. Different compositions were consisted of PCT, CRP and NLCR. The most valuable composition was chosen as which presented the highest discriminant capability between groups. A comparison of the diagnostic accuracy of the biomarkers, alone and in combination, was made by receiver operating characteristics (ROC) curves analysis by calculating the area under the curves (AUROC). For comparison of AUROCs, Mann-Whitney U test for two correlated ROC curves was used. All tests were two-sided, and $p < 0.05$ was considered statistically significant. The statistical analysis and graph construction were performed using SPSS 23 and Stata 12.

Results

General characteristics

A total of 659 episodes in adult patients suspected with HAP or non-infection admitted to the ICU at the First Affiliated Hospital of Nanjing Medical University were enrolled. Among total enrolled population, 66 patients were excluded from the analysis of the data due to certain exclusion criteria (Figure 1).

General characteristics of the overall population were displayed in Table 1. As a severity score for evaluation of the disease, APACHE II in HAP group was significantly higher than that of non-infection group (Table 1). Apart from this, most biomarkers including NLCR, PCT, CRP and WBC in HAP group significantly elevated compared to non-infection group, as described in Table 1.

The incidence of cardiovascular co-morbid conditions on admission to the ICU was lower in patients of non-infection than in HAP group. On the other hand, the incidence of malignancies was much higher in

non-infection group. The co-morbid disease profile was presented in Table 1 Additionally, the surgery operation incidence in non-infection group was much higher than that of HAP group, also described in Table 1.

Microorganisms profile

Positive cultures of the microbiological samples taken within 48 h of admission were reported in all episodes of HAP group patients, among which 324 cases of microorganisms were isolated. For all analyzed cases, 237 isolates of bacterial infection were found in 237 episodes of patients, with 27 isolates of gram-positive organisms and 210 isolates of gram-negative organisms. Apart from these, 83 isolates of fungi and 3 detections of viruses or antibodies had been identified. The detected microorganism profile has been shown in Table 2.

Diagnostic performance of the markers

Serum levels of various biomarkers between different groups were compared to determine the discriminant capability. Our study showed that PCT, CRP, NLCR and WBC were all distinguishable between two groups. However, serum lactate (LAC) and neutrophil % (NE) did not present any difference between these two groups. Compared to NLCR, both PCT and CRP levels showed good differential ability between non-infection and HAP group (Figure 2).

In the ROC curve analysis, single biomarkers such as CRP (AUC 0.685; 95% CI 0.641 - 0.730) and PCT (AUC 0.661; 95% CI 0.615 - 0.707) presented to have greater potential to differentiate HAP with non-infection group than NLCR (AUC 0.626; 95% CI 0.581 - 0.671), WBC (AUC 0.641; 95% CI 0.596 - 0.685) and NE (AUC 0.623; 95% CI 0.577 - 0.668). Compared to single biomarkers, combined markers showed better discriminant ability and diagnostic performance between the two groups (Figure 3).

As analyzed above, LAC in verified HAP patients did not present to be different from those in non-infective patients, based on the median (interquartile) analysis (Table 1 and Figure 2), and AUROC calculation.

We tested all the possible compositions of single biomarkers and displayed the top 5 AUROCs of composite biomarkers in Figure 3. The results showed the top five combination had no difference among each other according to AUROC analysis (Figure 3). Then for the purpose of easy accessibility, the combination of NLCR-CRP-WBC (AUC 0.690; 95% CI 0.646 - 0.734) and PCT-CRP-WBC (AUC 0.690; 95% CI

0.644 - 0.737) were proved be the most valuable composition in this study, as other combinations involved four or five single biomarkers (Figure 3).

Survival and mortality

The overall 28-day mortality rates of enrolled population were 25.3% (n = 150), 30.7% (n = 104) in HAP group and 18.1% (n = 46) in non-infection group. The mortality rate in HAP group was significantly higher than that of non-infection group.

In statistical analysis of 28-day survival in HAP group, NLCR, CRP and NE were much elevated in the non-survival population, indicating all these markers might have potential to predict prognosis of HAP patients (Figure 4). Meanwhile, the ROC analysis displayed that CRP (AUC 0.704; 95% CI 0.644 - 0.765) had the greatest discriminant ability to predict 28-day mortality as a single marker. Other single markers such NLCR, PCT, WBC and NE also showed good predictive value on outcomes (Figure 5).

In regard to composite biomarkers, the composition of NLCR-CRP-WBC presented to be the most valuable to predict mortality of HAP patients as its AUROC (AUC 0.720; 95% CI 0.660 - 0.780) was the best among all compositions (Figure 5). Other combination of biomarkers like NLCR-CRP (AUC 0.709; 95% CI 0.649 - 0.768) and CRP-WBC (AUC 0.711; 95% CI 0.650 - 0.772) also presented to be as potent as NLCR-CRP-WBC but with easier accessibility and simpler combination. Compared to most single biomarkers, combined markers showed better discriminant ability and diagnostic performance between the survivals and non-survivals. We tested all the possible compositions of single biomarkers and displayed the top 5 AUROCs of composite biomarkers in Figure 5.

Discussion

Over the past few years, numerous researches have investigated the clinical value of various biomarkers in diagnosis, prognosis and stratification of pneumonia [25]. Many studies have focused on the significance of single biomarkers, meanwhile interests in multiple biomarkers have increased, especially in severity evaluation of infective conditions, such as sepsis, septic shock and CAP. Contradicted conclusions have been presented due to inconsistent results drawn by small sample sized population [26,27]. In this study, we investigated the clinical value of NLCR, PCT and CRP alone and in combination with a large population consisting of 593 episodes of adult patients.

Here, we found that patients with HAP had higher levels of PCT and CRP than patients with non-infection (Table 1 and Figure 2). These patients showed greater severity with higher APACHE II scores (Table 1). This is in accordance with the data from Liu et al., who reported that PCT was associated with the severity of illness in patients with severe pneumonia and appeared to be a prognostic marker of morbidity and mortality comparable to the APACHE II score [27]. Our results suggested that CRP performed best in discriminating HAP with non-infection status as a single indicator (Figure 2,3). This agrees with the previous literature that PCT had been proved to be a valuable marker to predict mortality in septic patients [28].

PCT and CRP, as traditional biomarkers, have been intensely investigated for the past few years and the outcomes have been demonstrated contradicting [27,29]. This may be caused by small sample size, which could undermine the whole reliability of the results [30]. In our present study, PCT demonstrated a relatively high differential value (Figure 2, 3) for HAP and non-infection patients, indicating that the patients with a higher level of PCT could be likely diagnosed HAP in combination with clinical history. This agrees with Dr. Heggelund L's study that inflammatory biomarkers were associated with aetiology and predict outcomes in community-acquired pneumonia [5].

NLCR has been reported to be a indicator that correlated with the severity of series of diseases, and has been applied to predict prognosis of various clinical circumstances, ranging from colorectal cancer [17], glial tumor [31], sepsis and/or septic shock [32,18], to acute coronary syndrome [33]. In this study, we compared NLCR with other biomarkers on diagnostic performance and prognostic prediction. The conclusion was that NLCR could be a valuable marker in assistance of HAP diagnosis and prediction of mortality. On the other hand, conventional markers such as CRP and PCT both performed better than NLCR in discriminant of HAP and non-infection patients in this investigation, as shown in Figure 3. However, NLCR performed similar to both CRP and PCT in prediction of outcomes as described in Figure 5.

Regarding to AUROC analysis, CRP performed the best as a single biomarker to discriminate HAP with non-infection patients, and to predict 28-day mortality in HAP groups (Figure 3, 5). Meanwhile, PCT showed good potency to discriminate HAP with non-infection patients, and to predict 28-day mortality in HAP groups (Figure 3, 5). On the other hand, NLCR presented to have good diagnostic performance and outcome prediction ability, only its potency on diagnostic performance was weaker than CRP. We compared our results with previous literature [18, 19], it turns out many factors that affect the diagnostic performance of a biomarker might cause the controversies, thereby make it difficult and less viable to compare results from different studies.

In this study, we employed different methods to combine several biomarkers into one variable. Taken accessibility into account, the composition of NLCR-CRP-WBC had the most valuable diagnostic and prognostic performance than all other combinations based on AUROC analysis. Thus, we reported this combination as the major composition. Composite biomarker NLCR-CRP-WBC had been proved to be a reasonable predictor of 28-day mortality, indicating it might also be employed for risk stratification purposes. Thus this 3-marker composition could be widely applied to HAP patients for severity evaluation. This composite biomarker presented significantly higher AUROC than most single biomarkers, suggested that joint interpretation of multiple biomarkers could be ever more valuable in evaluation of HAP.

With respect to 28-day survival analysis, the survival rate of HAP group was much lower than that of non-infection group. Meanwhile, majority of the biomarkers in non-survivors presented to be significantly elevated. These data agree with previous observations that PCT in pneumonia patients correlated with the risk of death independent of the clinical risk assessment [34,35]. Besides, PCT was also proved to be capable of identifying unfavorable outcome in CAP and VAP (ventilator acquired pneumonia) patients in ICU [36,37,38]. While in clinical scenarios, PCT is more frequently used to guide antibiotic treatments. Although many reports supported NLCR as a valuable marker on severity evaluation and prognosis prediction of infectious diseases [14-16], our study brought up a different point of view in this aspect. Compared with conventional biomarkers such as CRP and PCT, NLCR presented to have moderate potency in diagnostic and prognostic performance of HAP.

Limitations of the study

Several limitations of this study rendered our concerns. First, patients with antibiotic treatment were not excluded from this study. Therefore, false negative results may be generated leading to underestimation of the severity. Second, the clinical diagnosis of HAP may be lack of accuracy in some cases, where there were no consistent changes on chest imaging, or there might be false negative results of microbiological sampling in patients receiving broad-spectrum antibiotics for a clinical diagnosis of HAP, or there might be positive results of microorganisms to be diagnosed as HAP, only in fact due to certain inflammation status combined with hospital acquired bacterial colonization instead of bacterial infection. Thirdly, in regard to non-infection group, this was true only for the admission period, because these patients could have infection afterwards. In this study we only evaluated the data of patients at admission. Although our study compared the sensitivity of biomarkers for HAP, the conclusion may not apply to patients suffered with any other severe infections, such as infections of cholecyst, skin and soft tissue, urinary system, abdomen or central nervous system.

Conclusion

In patients with HAP, conventional biomarkers such as CRP and PCT were associated with severity of the disease and could be good prognostic markers for prediction of morbidity and mortality in these patients. NLCR, as a recently explored biomarker, presented no advantage over conventional markers on severity evaluation and prognosis prediction of HAP. Both CRP and PCT performed better than NLCR on severity evaluation of HAP. Multiple biomarker composition could be a better choice for the purpose of disease diagnosis, severity evaluation, treatments guidance and prognosis prediction for HAP patients, especially the NLCR-CRP-WBC composition, as it was provided with easy access, simple interpretation and reliable quality.

List Of Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II; AUROC: Area under the ROC curve; CAP: community acquired pneumonia; CI: confidence interval; CRP: C-reactive protein; EIA: enzyme immunoassay; HAP: hospital acquired pneumonia; iMV: invasive mechanical ventilation; IRB: institutional review boards; LAC: lactate; NE: neutrophil %; NLCR: neutrophil-lymphocyte count ratio; PCT: procalcitonin; PCR: polymerase chain reaction; ROC: receiver operating characteristic; WBC: white blood cell.

Declarations

Ethics approval and consent to participate

We have received ethical approval (2020-SR-055) from the institutional review boards (IRBs) at the First Affiliated Hospital of Nanjing Medical University. Since this study does not contain protected health information and all data were anonymously used, a waiver of the requirement for informed consent was approved by the IRBs. Individual patients consent was not obtained since all data used in this study were acquired retrospectively from the laboratory information system without any additional sampling or laboratory analysis.

Consent for publication

Yes. We the authors all give consent for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NZ retrieved the data according to the background of non-infection and the hospital acquired pneumonia. YH analyzed and interpreted the data, constructed the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of the overall population

	Non-infection n = 254	HAP n = 339
Age (years)	66.6 ± 17.1	71.0 ± 17.9 **
Sex (M / F)	152 / 102	252 / 87 *
WBC abnormalities, n, (%)	54 (21.3%)	130 (38.2%) *
NE abnormalities, n, (%)	183 (72.0%)	254 (74.7%) *
APACHE II score (mean ± sd)	17.7 ± 5.9	21.7 ± 6.1 ***
NLCR	10.2 ± 9.8	13.0 ± 17.1 *
PCT (ng/ml)	0.75 ± 3.25	4.60 ± 15.97 ***
CRP (mg/ml)	45.8 ± 50.6	73.3 ± 79.6 ***
Blood lactate (mmol/l)	1.6 ± 1.3	1.5 ± 0.8
Surgery, n, (%)	100 (39.4%)	87 (25.6%) **
28 days survival, n, (%)	205 (80.7%)	233 (68.5%) **
Diabetes mellitus, n, (%)	5 (2.0%)	0 (0) *
Cardiovascular disease, n, (%)	28 (11.0%)	18(5.3%) *
Hypertension, n, (%)	5 (2.0%)	1(0.3%) *
Malignancies, n, (%)	54(21.3%)	10 (2.9%) ***
COPD, n, (%)	10(3.9%)	17 (5.0%)
Liver cirrhosis, n, (%)	2 (0.8%)	0 (0)
Renal failure, n, (%)	2(0.8%)	16 (4.7%) **

Data were expressed as Mean ± standard deviation or number (percentage) of current group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs non-infection group. WBC: white blood count; NE: neutrophil; NLCR: neutrophil lymphocyte count ratio; PCT: procalcitonin; CRP, C-reactive protein; HAP, hospital acquired pneumonia; COPD, chronic obstructive pulmonary disease.

Table 2. Microorganism profile for the patients in the study cohort

	28-day survival n = 235	Mortality n = 104	P value
Gram-positive isolates (n, %)	**16 (6.8%)**	**11 (10.6%)**	**0.2772**
S.Aureus	12 (5.1%)	10 (9.6%)	0.1505
MRSA	2 (0.9%)	0 (0)	1
Streptococcus spp.	1 (0.4%)	0 (0)	1
Enterococcus spp.	2 (0.9%)	1 (1.0%)	1
Other	1 (0.4%)	0 (%)	1
Gram-negative isolates (n, %)	**158 (67.2%)**	**52 (50.0%)**	**0.0035**
Acinetobacter baumannii	76 (32.3%)	37 (35.6%)	0.6175
Klebsiella spp.	59 (25.1%)	26 (25.0%)	1
Pseudomonas spp.	50 (21.3%)	13 (12.5%)	0.0687
Enterobacter spp.	24 (10.2%)	6 (5.8%)	0.2177
S. maltophilia	16 (6.8%)	3 (2.9%)	0.2018
Other	9 (3.8%)	4 (3.8%)	1
Fungi isolates (n, %)	**55 (23.4%)**	**28 (26.9%)**	**0.4959**
Candida albicans	28 (11.9%)	17 (16.3%)	0.2985
Candida glabrada	16 (6.8%)	2 (1.9%)	0.0702
Candida tropicalis	7 (3.0%)	4 (3.8%)	0.7423
Other	4 (1.7%)	4 (3.8%)	0.2556
Virus isolates (n, %)	**2 (0.9%)**	**1 (1.0%)**	1
Tuberculosis isolates (n, %)	**1 (0.4%)**	**0 (0)**	1

Data were presented as number of isolates (percentage of current group), not number of patients. S.Aureus, staphylococcus aureus; MRSA, methicillin-resistant staphylococcus aureus; S. maltophilia, Stenotrophomonas maltophilia; spp., species.

Figures

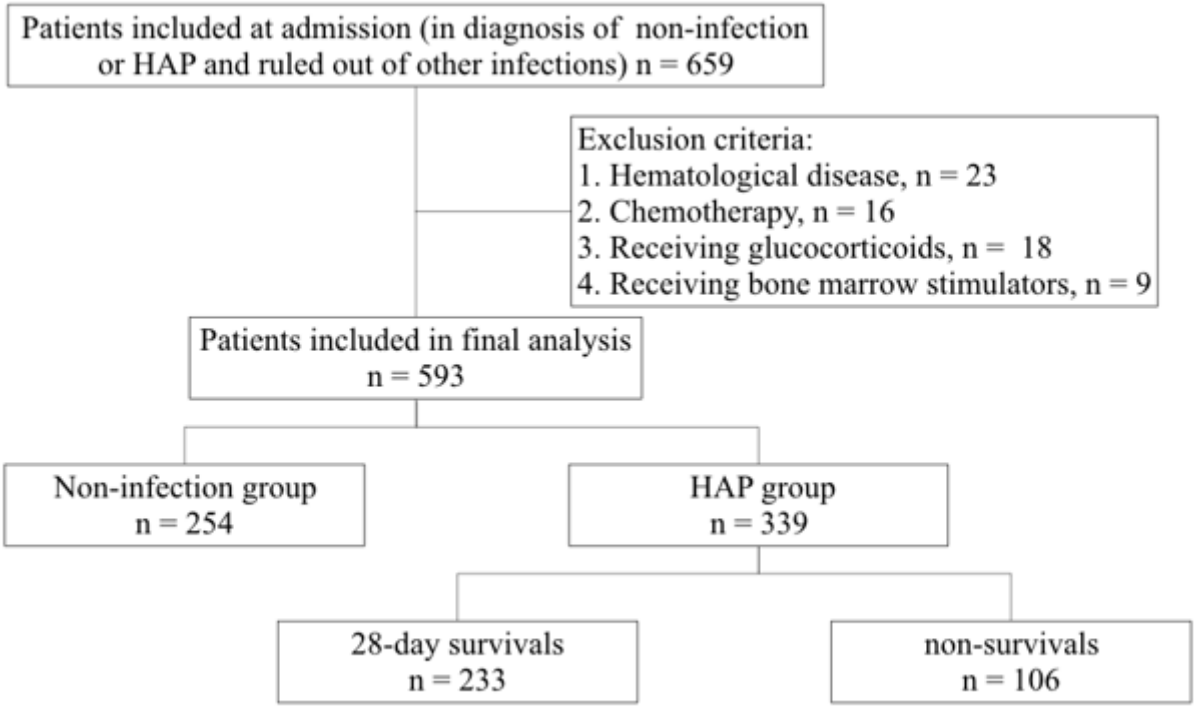


Figure 1

Enrollment flowchart. Patients in diagnosis of non-infection or HAP were included at admission. Pa-tients with other infection, such as infection of cholecyst, skin and soft tissue, urinary system, abdo-men or central nervous system were all excluded.

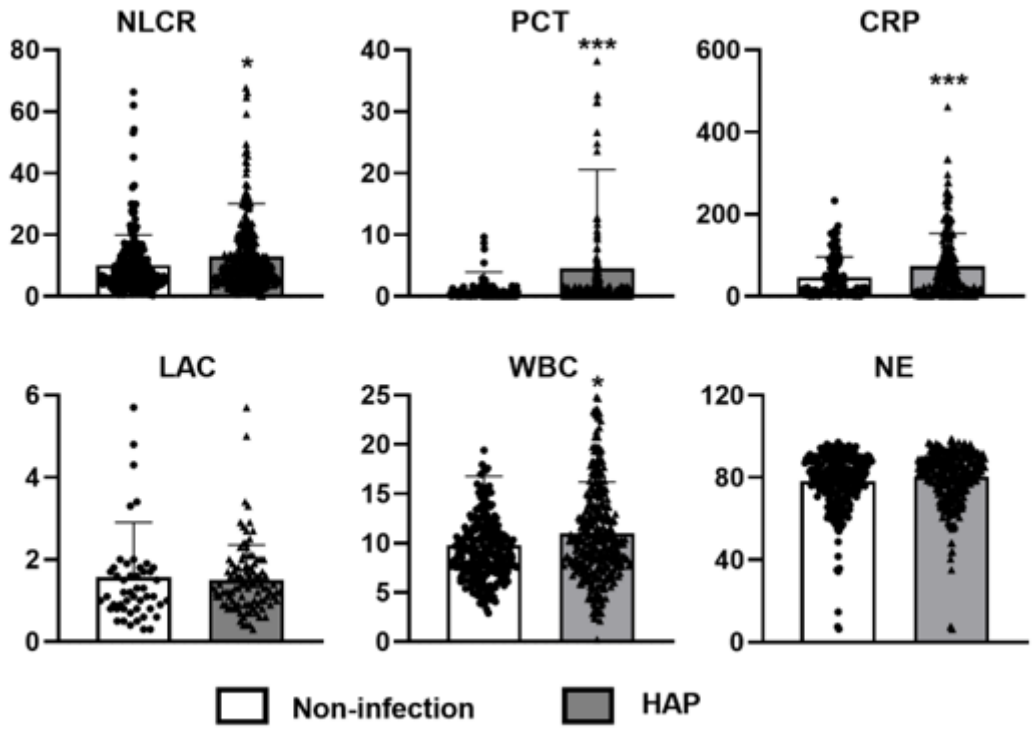
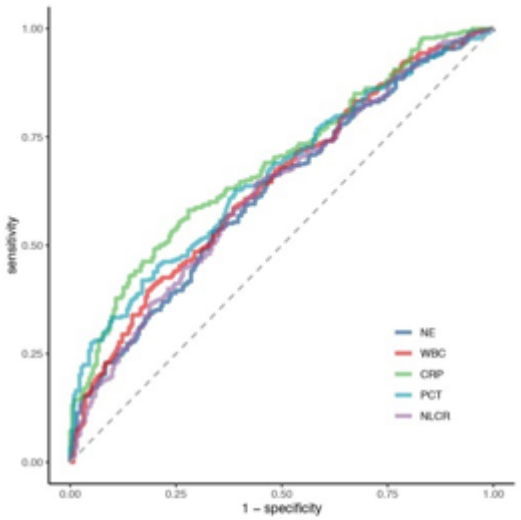


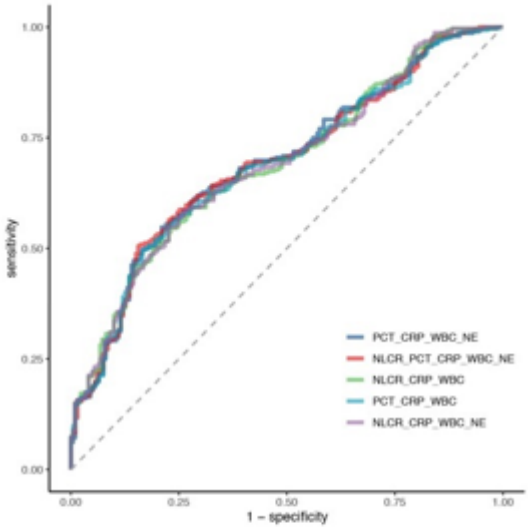
Figure 2

Single biomarker levels of NLCR, PCT, CRP, LAC, WBC, and NE in non-infection and HAP group. *p < 0.05, ***p < 0.001 vs non-infection group. NLCR: neutrophil lymphocyte count ratio; PCT: pro-calcitonin; CRP, C-reactive protein; LAC: lactate; WBC: white blood count; NE: neutrophil %; HAP, hospital acquired pneumonia.



Marker[a]	AUROC	95% CI	*P* value[b]
NE	0.623	(0.577, 0.668)	0.0006
WBC	0.641	(0.596, 0.685)	0.0061
CRP	0.685	(0.641, 0.730)	Ref
PCT	0.661	(0.615, 0.707)	0.2968
NLCR	0.626	(0.581, 0.671)	0.0022

Abbreviation: CI, confidence interval; Ref, reference.
[a]single marker.
[b]P value was calculated by DeLong's test.



Marker[a]	AUROC	95% CI	*P* value[b]
PCT_CRP_WBC_NE	0.694	(0.648, 0.740)	Ref
NLCR_PCT_CRP_WBC_NE	0.693	(0.646, 0.740)	0.6143
NLCR_CRP_WBC	0.690	(0.646, 0.734)	0.0196
PCT_CRP_WBC	0.690	(0.644, 0.737)	0.2140
NLCR_CRP_WBC_NE	0.690	(0.645, 0.734)	0.0125

Abbreviation: CI, confidence interval; Ref, reference.
[a]combined markers.
[b]P value was calculated by DeLong's test.

Figure 3

Receiver operator characteristic (ROC) curve for HAP discrimination with non-infection group, and area under the ROC (AUROC) for the single and top five combined biomarkers evaluated in this study. NE: neutrophil%; WBC: white blood count; CRP, C-reactive protein; PCT: procalcitonin; NLCR: neutrophil lymphocyte count ratio.

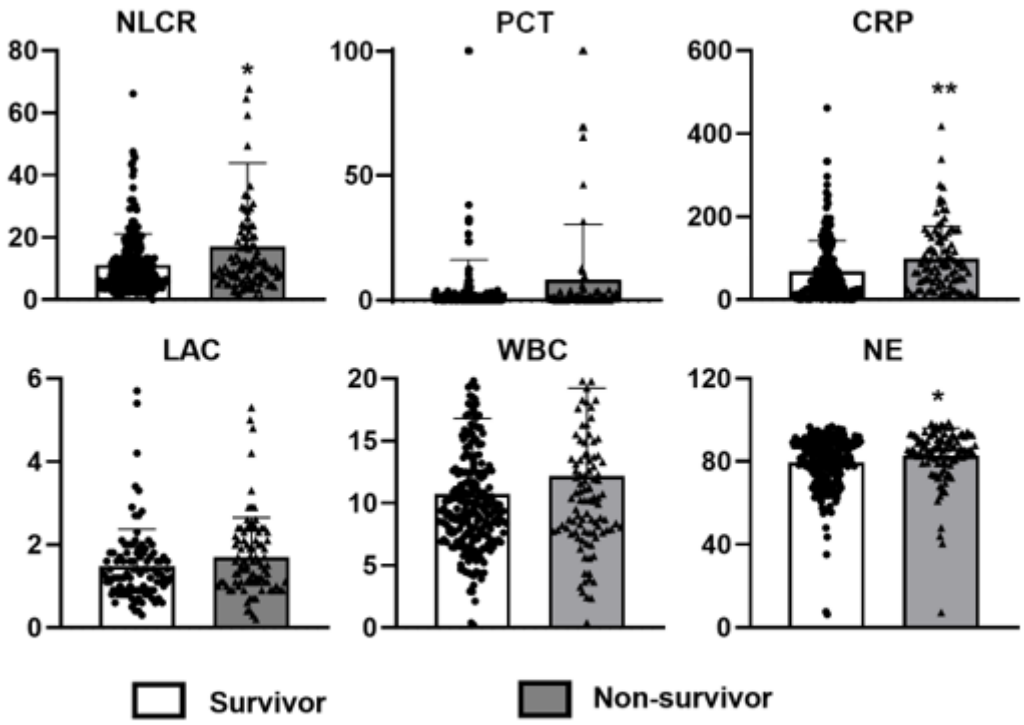
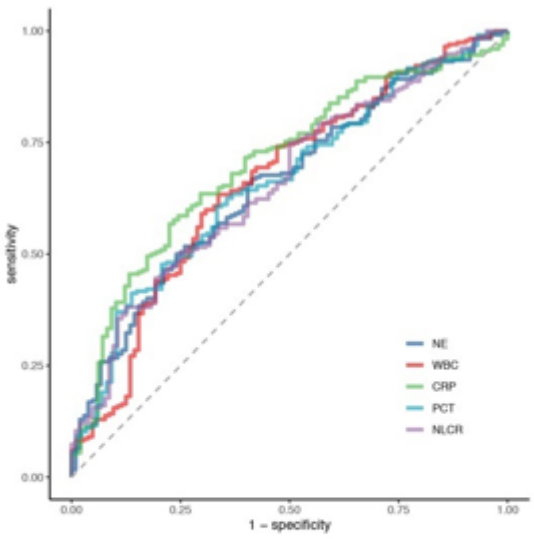


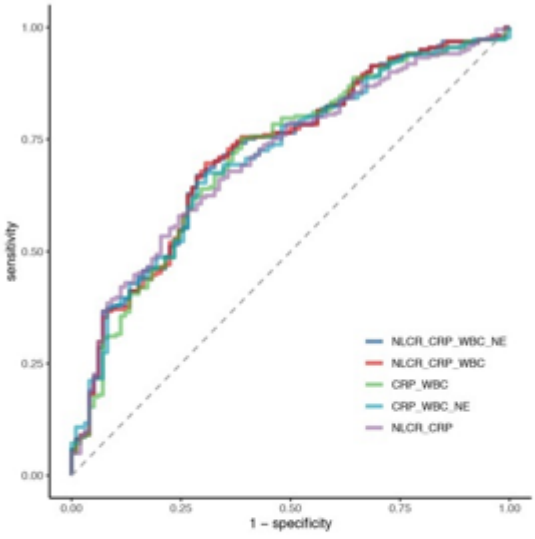
Figure 4

Single biomarker levels of NLCR, PCT, CRP, LAC, WBC and NE in 28-d survivals and non-survivals of HAP group. *p < 0.05, **p < 0.01 vs 28-d survivals. NLCR: neutrophil lymphocyte count ratio; PCT: procalcitonin; CRP, C-reactive protein; LAC: lactate; WBC: white blood count; NE: neutrophil %.



Marker[a]	AUROC	95% CI	*P* value[b]
NE	0.657	(0.596, 0.718)	0.1719
WBC	0.664	(0.600, 0.727)	0.1755
CRP	0.704	(0.644, 0.765)	Ref
PCT	0.662	(0.596, 0.727)	0.2816
NLCR	0.659	(0.597, 0.720)	0.1632

Abbreviation: CI, confidence interval; Ref, reference.
[a]single marker.
[b]P value was calculated by DeLong's test.



Marker[a]	AUROC	95% CI	*P* value[b]
NLCR_CRP_WBC_NE	0.720	(0.660, 0.779)	Ref
NLCR_CRP_WBC	0.720	(0.660, 0.780)	0.9060
CRP_WBC	0.711	(0.650, 0.772)	0.4345
CRP_WBC_NE	0.711	(0.651, 0.771)	0.3076
NLCR_CRP	0.709	(0.649, 0.768)	0.3419

Abbreviation: CI, confidence interval; Ref, reference.
[a]combined markers.
[b]P value was calculated by DeLong's test.

Figure 5

Receiver operator characteristic (ROC) curve for 28-day survival discrimination with non-survival in HAP group and area under ROC (AUROC) for the single and top five combined biomarkers evaluated in HAP group. NE: neutrophil %; WBC: white blood count; CRP, C-reactive protein; PCT: procalciton-in; NLCR: neutrophil lymphocyte count ratio.