Journal of
Anesthesia and Intensive Care
ISSN: 2769-7029

ScienceAssist International

Research Article | Open Access

Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), Platelet-to-Lymphocyte Ratio (PLR) and Red Cell Distribution Width (RDW) to Predict Outcome and Differentiate between Viral and Bacterial Pneumonia in the Intensive Care Unit: A Retrospective Study

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Received: October 30, 2021; Accepted: November 23, 2021; Published: November 30, 2021

Abstract

Introduction: Neutrophil-to-Lymphocyte ratio (NLR), Monocyte-to-Lymphocyte ratio (MLR), Platelet-to-Lymphocyte Ratio (PLR), and Red Cell Distribution Width (RDW) are emerging biomarkers to predict outcome in general ward patients. However, their role in the prognostication of critically ill patients with pneumonia is unclear.

Material and Methods: 216 adult patients were enrolled over 2 years. They were classified into viral and bacterial pneumonia groups, represented by influenza A virus and Streptococcus pneumonia, respectively. Demographics, outcomes, and laboratory parameters were analyzed. The prognostic power of blood parameters was determined by their respective area under the receiver operating characteristic curve (AUROC). Their performance was compared with the APACHE IV score. Discriminant ability in differentiating viral and bacterial aetiologies was studied.

Results: Viral and bacterial pneumonia were identified in 111 and 105 patients, respectively. In predicting hospital mortality, the APACHE IV score was the best prognostic score compared with all the studied blood parameters (AUC 0.769, 95% CI 0.705-0.833). In classification tree analysis, the most significant predictor of hospital mortality was the APACHE IV score (adjusted P=0.000, χ^2 = 35.591). Mechanical ventilation was associated with higher hospital mortality in those patients with low APACHE IV score <=70 (adjusted P=0.014, χ^2 = 5.999). In patients with high APACHE IV score >90, age (>78, adjusted P=0.007, χ^2 = 11.221) and thrombocytopenia (platelet count <=128, adjusted P=0.004, χ^2 = 12.316) were predictive of higher hospital mortality.

Conclusion: Novel inflammatory biomarkers were not comparable to the APACHE IV score in predicting hospital mortality. In differentiation between viral and bacterial pneumonia, there is no ideal biomarker.

Key words: Neutrophil-to-lymphocyte ratio; Mortality; Intensive care unit; Viral pneumonia; Bacterial pneumonia

ABBREVIATIONS

NLR: Neutrophil-To-Lymphocyte Ratio, MLR: Monocyte-To-Lymphocyte Ratio, PLR: Platelet-To-Lymphocyte Ratio, RDW: Red Cell Distribution Width

INTRUDUCTION

Pneumonia is a frequent cause of admission to the intensive care unit (ICU). An increasing number of biomarkers have been developed to identify patients at risk of severe

disease. The neutrophil-to-lymphocyte ratio (NLR) is a novel inflammatory biomarker increasingly studied in different fields of medicine [1]. It increases in proportion to the degree of physiological stress, a property that has prognostic value in predicting outcomes. Studies have shown an association between NLR and patient outcomes in septic and bacteremic patients in the Emergency Department and the general wards [2-5], as well as acute coronary syndrome, acute pancreatitis, and rheumatic diseases [6-12]. Its prognostic significance in the ICU, however, remains uncertain. Like the NLR, monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and red cell distribution width (RDW) are described and evaluated as inflammatory biomarkers in a variety of medical conditions.

The use of NLR may also have diagnostic significance. In bacterial infections, neutrophilia and bandemia develop, resulting in a raised NLR. A higher NLR may indicate that an infection is bacterial rather than viral in origin.

Our study aims to evaluate (1) the prognostic accuracy of these simple biomarkers in predicting hospital mortality, with comparison to Acute Physiology and Chronic Health Evaluation (APACHE) IV score and (2) their diagnostic power in differentiating pneumonia aetiologies.

MATERIALS AND METHODS

Study Design and Data Collection

This retrospective analysis was conducted from January 1, 2017, to June 30, 2019, in Pamela Youde Nethersole Eastern Hospital (PYNEH), a 1700-bed regional hospital in Hong Kong. Patients admitted to the ICU in PYNEH with influenza A, or pneumococcal pneumonia were enrolled. Patients with co-infection by both virus and bacteria, age less than 18, and insufficient data were excluded. Retrospective analysis of medical records, data in clinical management systems, and clinical information systems (IntelliVue Clinical Information Portfolio, Philips Medical, Amsterdam, Netherlands) was done.

The primary outcome was the ability of NLR in predicting hospital mortality. Secondary outcomes were the ability of MLR, PLR, and RDW to predict hospital mortality and the diagnostic performance of NLR, MLR, PLR, and RDW in discriminating viral from bacterial pneumonia.

Definitions

Diagnosis of pneumonia was based on clinical criteria: the presence of pulmonary infiltrates on chest radiograph at the time of admission, plus either new or increased cough with or without sputum production, or abnormal body temperature (temperature <36C or >38C), or abnormal leukocyte count (WCC <=4 or >=12 x10^6/L). Influenza A pneumonia was diagnosed by one or more upper or lower respiratory samples yielding influenza A virus by polymerase chain reaction (PCR). Pneumococcal pneumonia was defined by the growth of Streptococcus pneumoniae in blood culture or sputum culture or by the positivity of urinary antigen for Streptococcus pneumoniae.

Laboratory parameters included in the study were obtained from complete blood count (CBC) taken at 0hr and 48hr of admission. Delta value was obtained by subtraction of data at 0hr from data at 48hr. The individual variables obtained directly from CBC were white cell count (WCC), neutrophil count, lymphocyte count, monocyte count, platelet count, and red cell distribution width (RDW). Parameters derived from these variables included neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR).

Statistical Analysis

Demographics, clinical outcomes, and laboratory parameters were compared between hospital survivors and non-survivors and patients with viral and bacterial pneumonia. Categorical variables were expressed as the number of cases and percentages. Continuous variables were expressed as median ± interquartile range (IQR). Univariate analysis for categorical variables was compared using Fisher's exact test or Pearson chi-square test as appropriate. Continuous variables were compared by the Mann Whitney U test or Student t-test. Variables with $p<0.1$ in the univariate analysis were included in the multivariate analysis. Logistic regression analysis with backward stepwise elimination was used to assess independent predictors for hospital mortality. A $p<0.05$ was considered significant.

A comparison of the variables' prognostic and diagnostic accuracy was made using receiver operating characteristic (ROC) curves. Calculation of the area under the receiver operating characteristic curve (AUROC) was expressed, ranging from 0.5 to 1.0. Higher values show greater power in the discriminatory outcome.

A classification tree model was used to identify the predictors for hospital mortality. This data mining method classifies the studied population into subgroups of dependent variables based on the values of independent variables by using non-parametric testing. The splitting

method is called Exhaustive Chi-Squared Automatic Interaction Detector (CHAID). The analysis was conducted in a stepwise manner using the Pearson Chi-squared test. The variable with the smallest Bonferroni adjusted p-value and yielding the most significant split was chosen. Nodes were created that maximized group differences in the outcome. A terminal node was produced when the number of child nodes was below 2 or when the smallest adjusted p-value was insignificant. All analyses were performed using the Statistical Package for Social Sciences for Windows, version 27.0 (SPSS, Chicago, United States).

The sample size was calculated based on an average AUROC of 0.688 (average AUROC taken from 3 studies: 0.746 [13], 0.695 [14], and 0.622 [15]) for neutrophil-to-lymphocyte ratio (NLR) in predicting hospital mortality. With a type, I error of 0.05, power of 80%, an expected mortality rate of 12.5%, the calculated sample size is 189.

RESULTS

Baseline Characteristics and Clinical Outcomes

A total of 216 patients were enrolled during the 2 years. One hundred eleven patients had viral pneumonia, while 105 had bacterial pneumonia. Baseline characteristics and clinical outcomes are listed in Table 1. The median age was 69 (interquartile range 59-80). More than half (59%) were male. For medical co-morbidities, 64.6% (139/216) had hypertension, 35.2% (76/216) had diabetes mellitus, and 33.8% (73/216) had ischaemic heart disease. Nearly half of the population (49.1%, 106/216) had a chronic renal disease or end-stage renal failure. 5.6% (12/216) had an underlying hematological malignancy, while 2.8% (6/216) had a solid tumor. The median APACHE IV score was 91 (63-115). The median APACHE IV predicted risk of death was 0.39 (0.16-0.66). Most of the population (83.3%, 180/216) had septic shock. 69% (149/216) patients were mechanically ventilated, and 34.3% (74/216) required renal replacement therapy. The median intensive care unit (ICU) and hospital length of stay were 4 (1.8-9.7) and 13.3 (7.0-28.8), respectively.

Univariate analysis (Table 1) showed that diabetes mellitus (43.2% vs 26.7%, p=0.015) were more commonly found in patients with viral pneumonia. In comparison, patients with bacterial pneumonia were more likely to develop septic shock (94.3% vs 73%, p<0.001).

Comparison Between Survivors and Non-Survivors

The overall hospital mortality rate of the enrolled population was 31% (n=67). Univariate analysis (Table 2) showed that hospital non-survivors were older (median

Table 1. Comparison of patient demographics and outcome parameters between viral and bacterial pneumonia

	Total (N= 216)	Viral (N= 111)	Bacterial (N= 105)	P-value
Age	69 (59-80)	69 (55-81)	69 (60-79)	0.868
Male	129 (59.7)	61 (55.0)	68 (64.8)	0.166
Co-morbidities				
Diabetes mellitus	76 (35.2)	48 (43.2)	28 (26.7)	0.015
Hypertension	139 (64.6)	77 (69.4)	62 (59.0)	0.120
Ischaemic heart disease	73 (33.8)	44 (39.6)	29 (27.6)	0.084
COPD	30 (13.9)	16 (14.4)	14 (13.3)	0.846
Liver cirrhosis	3 (1.4)	1 (0.9)	2 (1.9)	0.613
CKD/ESRF	106 (49.1)	58 (52.3)	48 (45.7)	0.345
Solid tumour	6 (2.8)	1 (0.9)	5 (4.8)	0.111
Haematological malignancy	12 (5.6)	4 (3.6)	8 (7.6)	0.242
APACHE IV				
Score	91 (63-115)	90 (57-116)	93 (69-114)	0.390
Predicted risk of death	0.39 (0.16-0.66)	0.40 (0.13-0.67)	0.39 (0.17-0.62)	0.833
Presence of septic shock	180 (83.3)	81 (73.0)	99 (94.3)	<0.001
Mechanical ventilation	149 (69.0)	83 (74.8)	66 (62.9)	0.077
Renal replacement therapy	74 (34.3)	36 (32.4)	38 (36.2)	0.570
Length of stay (days)				
ICU	4.0 (1.8-9.7)	3.8 (1.7-10.7)	4.1 (1.8-8.3)	0.807
Hospital	13.3 (7.0-28.8)	13.2 (6.8-36.1)	13.5 (7.6-23.7)	0.851
Mortality				
ICU	46 (21.3)	20 (18.0)	26 (24.8)	0.248
Hospital	67 (31.0)	33 (29.7)	34 (32.4)	0.769

Abbreviations: COPD=chronic obstructive pulmonary disease; CKD/ESRF=chronic kidney disease/end-stage renal failure; APACHE IV=Acute Physiology and Chronic Health Evaluation IV

Table 2. Comparison between hospital survivors and non-survivors

	Total (N= 216)	Survivor (N=149)	Non-survivor (N=67)	P value
Age	69 (59-80)	65 (55-77)	78 (68-85)	<0.001
Male	129 (59.7)	85 (57.0)	44 (65.7)	0.294
Viral cause	111 (51.4)	78 (52.3)	33 (49.3)	0.769
Co-morbidities				
Diabetes mellitus	76 (35.2)	53 (35.6)	23 (34.3)	0.879
Hypertension	139 (64.6)	100 (67.1)	39 (58.2)	0.222
Ischaemic heart disease	73 (33.8)	47 (31.5)	26 (38.8)	0.351
COPD	30 (13.9)	21 (14.1)	9 (13.4)	1.000
Liver cirrhosis	3 (1.4)	2 (1.3)	1 (1.5)	1.000
CKD/ESRF	106 (49.1)	59 (39.6)	47 (70.1)	<0.001
Solid tumour	6 (2.8)	5 (3.4)	1 (1.5)	0.668
Haematological malignancy	12 (5.6)	5 (3.4)	7 (10.4)	0.051
APACHE IV				
Score	91 (63-115)	79 (53-103)	110 (93-135)	<0.001
Predicted risk of death	0.39 (0.16-0.66)	0.26 (0.11-0.52)	0.61 (0.43-0.85)	<0.001
Presence of septic shock	180 (83.3)	118 (79.2)	62 (92.5)	0.017
Mechanical ventilation	149 (69.0)	93 (62.4)	56 (83.6)	0.002
Renal replacement therapy	74 (34.3)	42 (28.2)	32 (47.8)	0.008
Length of stay (days)				
ICU	4.0 (1.8-9.7)	3.8 (1.7-9.5)	4.1 (2.0-11.0)	0.508
Hospital	13.3 (7.0-28.8)	14.1 (8.0-33.4)	11.1 (4.2-23.4)	0.012
WCC				
0hr	10.7 (6.4-15.6)	10.8 (6.8-16.3)	10.2 (4.6-15.1)	0.232
48hr	11.6 (8.2-17.5)	11.4 (8.5-17.1)	11.8 (7.3-18.1)	0.952
Delta	0.5 (-2.6-5.7)	0.4 (-2.9-5.5)	0.9 (-1.3-6.1)	0.252
Neutrophil				
0hr	9.0 (5.4-13.0)	9.5 (5.6-13.7)	8.4 (4.1-11.7)	0.118
48hr	10.3 (7.0-16.1)	10.3 (7.2-16.0)	10.6 (6.3-16.4)	0.719
Delta	0.2 (-1.5 – 4.8)	0.0 (-2.1-4.4)	0.7 (-1.0 – 5.5)	0.166
Lymphocyte				
0hr	0.7 (0.4-1.2)	0.8 (0.5-1.2)	0.6 (0.3-1.4)	0.058
48hr	0.8 (0.5-1.1)	0.9 (0.5-1.2)	0.6 (0.3-0.9)	0.004
Delta	0.0 (-0.2-0.2)	0.0 (-0.2-0.3)	0.0 (-0.5- 0.2)	0.090
Monocyte				
0hr	0.4 (0.2-0.7)	0.4 (0.2-0.6)	0.3 (0.1-0.7)	0.155
48hr	0.4 (0.2-0.6)	0.5 (0.3-0.6)	0.2 (0.1-0.6)	0.002
Delta	0.0 (-0.1-0.2)	0.0 (-0.1-0.2)	0.0 (-0.1-0.1)	0.111
Platelet				
0hr	171 (121-224)	178 (131-228)	144 (89-206)	0.002
48hr	148 (91-197)	164 (117-210)	96 (57-156)	<0.001
Delta	-21 (-54 – 6)	-17 (-47-12)	-31 (-64 - -6)	0.018
NLR				
0hr	11.6 (5.6-18.9)	12.0 (5.7-19.9)	10.7 (5.5-17.9)	0.694
48hr	14.3 (8.0-23.7)	13.4 (7.3-22.1)	15.4 (9.4-31.4)	0.088
Delta	0.6 (-3.0 – 8.4)	0.0 (-3.4-5.9)	3.8 (-1.9-11.7)	0.016
MLR				
0hr	0.4 (0.2-0.8)	0.4 (0.2-0.8)	0.5 (0.2-0.8)	0.930
48hr	0.5 (0.3-0.8)	0.5 (0.3-0.8)	0.4 (0.3-0.9)	0.403
Delta	0.0 (-0.2-0.2)	0.0 (-0.1-0.2)	0.0 (-0.2-0.3)	0.917
RDW				
0hr	14.1 (13.3-15.4)	13.9 (13.2-15.0)	14.7 (13.7-15.8)	0.001
48hr	14.5 (13.7-15.6)	14.2 (13.5-15.4)	15.1 (14.2-16.4)	<0.001
Delta	0.3 (0.0-0.6)	0.2 (0.0 -0.5)	0.3 (0.0-0.6)	0.511
PLR				
0hr	231 (132-362)	235 (135-338)	218 (122-419)	0.671
48hr	195 (120-294)	200 (126 – 300)	187 (92-274)	0.342
Delta	-23 (-140 – 53)	-18 (-107 – 55)	-47 (-203 – 46)	0.163

Abbreviations: COPD=chronic obstructive pulmonary disease; CKD/ESRF=chronic kidney disease/end-stage renal failure; APACHE IV=Acute Physiology and Chronic Health Evaluation IV; WCC=white cell count; NLR=neutrophil-to-lymphocyte ratio; MLR=monocyte-lymphocyte ratio; RDW=red cell distribution width; PLR=platelet-to-lymphocyte ratio

Delta is defined by the difference between 0hr and 48 hr data (48hr minus 0hr)

78 vs 65, p<0.001), more likely to suffer from chronic kidney disease or end-stage renal failure (70.1% vs 39.6%, p<0.001) and haematological malignancy (10.4% vs 3.4%, p=0.051). Hospital non-survivors also had higher APACHE IV score (110 vs 79, p<0.001), APACHE IV predicted risk of death (0.61 vs 0.26, p<0.001), were more likely to have septic shock (92.5% vs 79.2%, p=0.017), receive mechanical ventilation (83.6% vs 62.4%, p=0.002), require renal replacement therapy (47.8% vs 28.2%, p=0.008), and had shorter hospital length of stay (11.1 vs 14.1, p=0.012).

Univariate analysis of laboratory parameters (Table 2) showed that lymphocyte at 0hr, 48hr and its delta, monocyte at 48hr and platelet at 0hr, 48hr and its delta were significantly lower in non-survivors. NLR at 48hr and its delta and RDW at 0 hr and 48hr were significantly higher in non-survivors.

Prognostic Performance of Laboratory Parameters

The prognostic power of the significant parameters identified in the univariate analysis was compared with the APACHE IV score, and APACHE IV predicted risk of death by the ROC analysis (Table 3). APACHE IV predicted risk of death (AUC 0.776, 95% CI 0.713-0.84) and APACHE IV score (AUC 0.769, 95% CI 0.705-0.833) had the highest discriminatory ability for prediction of hospital mortality. Platelet at 48 hr performed the best among the laboratory parameters in predicting hospital mortality (AUC 0.721, 95% CI 0.643-0.798). RDW at 48hr (AUC 0.661, 95% CI 0.582-0.740), RDW at 0hr (AUC 0.636, 95% CI 0.555-0.717), platelet at 0hr (AUC 0.632, 95% CI 0.55-0.713) and monocyte at 48hr (AUC 0.63, 95% CI 0.542-0.718) had similar performance in their predictive value.

Variables that were associated (p<0.1) with hospital mortality in the initial univariate analysis (Table 2) were included in the multivariate analysis. Table 4 shows the logistic regression analysis of predictors of hospital mortality. Independent predictors of hospital mortality included age (odds ratio 1.052, p=0.001), APACHE IV score (OR 1.020, p=0.001), RDW at 48 hr (OR 1.268, p=0.011), delta NLR (OR 1.019, p=0.051) and platelet at 0hr (OR 0.994, p=0.013). The Hosmer-Lemeshow test

Table 3. Area under receiver operating characteristic curves (AUROC) for prediction of hospital mortality.

	AUROC	SE	95% CI	HL test
APACHE IV Risk of Death	0.776	0.032	0.713-0.84	0.637
APACHE IV Score	0.769	0.033	0.705-0.833	0.055
Platelet 48hr	0.721	0.039	0.643-0.798	0.058
Age	0.711	0.037	0.638-0.784	0.852
RDW48hr	0.661	0.04	0.582-0.740	0.715
RDW0hr	0.636	0.041	0.555-0.717	0.716
Platelet 0hr	0.632	0.041	0.55-0.713	0.293
Monocyte48hr	0.63	0.045	0.542-0.718	0.068
Lymphocyte48hr	0.621	0.043	0.536-0.706	0.074
Delta NLR	0.603	0.044	0.517-0.688	0.079
Delta platelet	0.601	0.041	0.52-0.682	0.707

Abbreviations: APACHE IV=Acute Physiology and Chronic Health Evaluation IV; NLR=neutrophil-to-lymphocyte ratio; RDW=red cell distribution width; AUROC= area under receiver operating characteristic curves; SE=; CI=confidence interval

HL test: Hosmer-Lemeshow goodness-of-fit test

Table 4. Logistic regression analysis using backward stepwise (likelihood ratio) for independent predictor of hospital mortality

	OR	95% CI	P value
Age	1.052	1.022-1.083	0.001
APACHE IV score	1.020	1.008-1.032	0.001
RDW at 48hr	1.268	1.056-1.523	0.011
Delta NLR	1.019	1.000-1.039	0.051
PLT at 0hr	0.994	0.990-0.999	0.013

a) Factors included within the model building: Age, APACHE IV score, presence of chronic kidney disease, presence of haematological malignancy, presence of septic shock, use of mechanical ventilation, use of renal replacement therapy, lymphocyte at 0hr and 48hr, delta lymphocyte, monocyte at 48hr, platelet at 0hr and 48hr, delta platelet, neutrophil lymphocyte ratio at 48hr, delta NLR, RDW at 0hr and 48hr (Factor selection based on the univariate analysis result from Table 2 with p<0.1 and without collinearity)

b) Logistic regression: Hosmer-Lemeshow test chi-square 4.455, df 8, p=0.814, AUROC of the model: 0.830, 95% CI 0.772-0.888)

was examined to ensure the goodness of fit of statistical models, with a P-value of 0.814, which indicated good calibration and model fit.

The composite of the 5 parameters in Table 4 was referred to as Model 1. Figure 1 compared the prognostic performance of Model 1 and APACHE IV score by the ROC analysis. Model 1, being a composite of five independent predictors, showed superiority in predicting hospital mortality (AUC 0.830, 95% CI 0.772-0.888) over APACHE IV score alone (AUC 0.769, 95% CI 0.705-0.833).

Classification Tree Analysis

The classification tree model (Figure 2) analyzed the determinant factors that predict hospital mortality. The most significant predictor was the APACHE IV score (adjusted P=0.000, χ^2 = 35.591). For patients with APACHE IV score <=70, those requiring mechanical ventilation had increased hospital mortality (adjusted P=0.014, χ^2 = 5.999, hospital mortality rate of 14% vs 0% compared with those not requiring mechanical ventilation). For patients with APACHE IV score >90 and older with age >78 (adjusted P=0.007, χ^2 = 11.221), the hospital mortality rate was up to 67.4%. For patients with APACHE IV score >90 and younger with age <=78, platelet count (adjusted P=0.004, χ^2 = 12.316) became an important determinant of their mortality. Those with platelet count <=128 at 0 hr had higher hospital mortality (59.3% vs 16.7%) when compared with those patients with platelet count >128.

Diagnostic Performance of Laboratory Parameters

Diagnostic performance of different laboratory parameters to differentiate between viral and bacterial pneumonia were analyzed. Patients with viral pneumonia had lower white cell count (WCC) at 48 hr (9.9 vs 13.6, p<0.001), neutrophil count at 48 hr (8.8 vs 11.6, p=0.001), and delta red cell distribution width (RDW, 0.2 vs 0.3, p=0.013) when compared with patients suffering from bacterial pneumonia (Table 5). In the receiver operating characteristic (ROC) curve analysis of these parameters (Table 6), WCC at 48 hr (AUC 0.648; 95% CI 0.572-0.722) had a greater ability to differentiate viral from bacterial pneumonia than neutrophil at 48hr (AUC 0.627, 95% CI 0.552-0.702) and delta RDW (AUC 0.594, 95% CI 0.518-0.670). Figure 3 displays the respective ROC curves of these parameters.

DISCUSSION

Neutrophil-to-Lymphocyte Ratio (NLR) in the Prediction of Hospital Mortality

The complete blood count is frequently used to evaluate sepsis, focusing on the white cell count (WCC) and the presence of left shift or bandemia [1]. However, abnormal

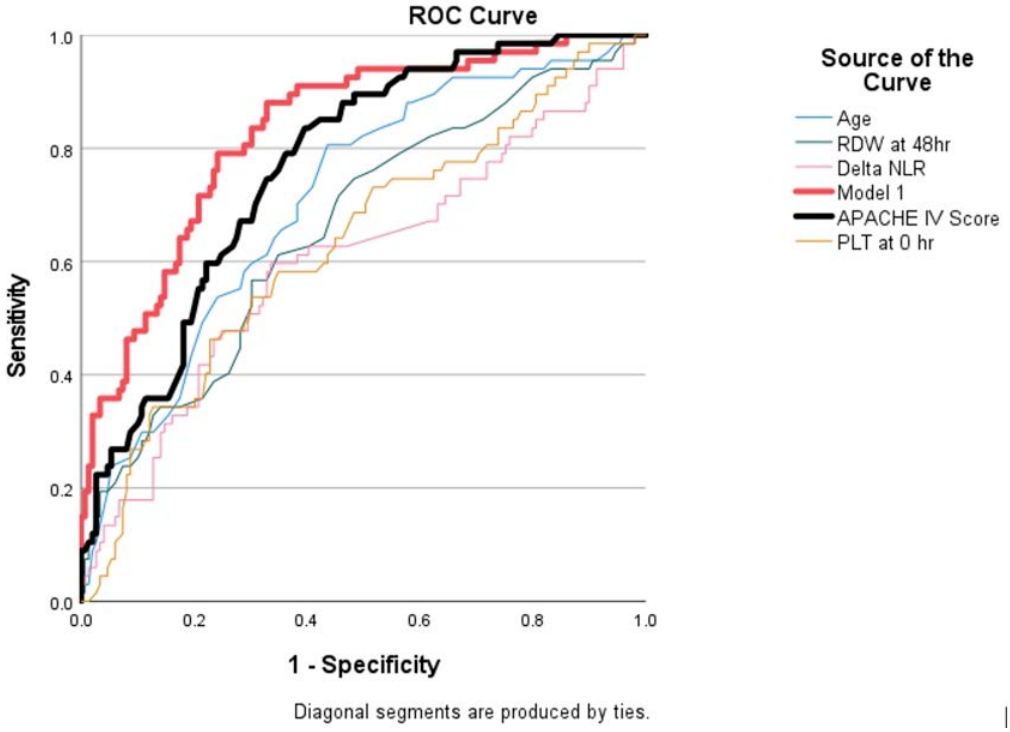

Figure 1: Receiver operating characteristic (ROC) curves to compare performance of APACHE IV score and Model 1.

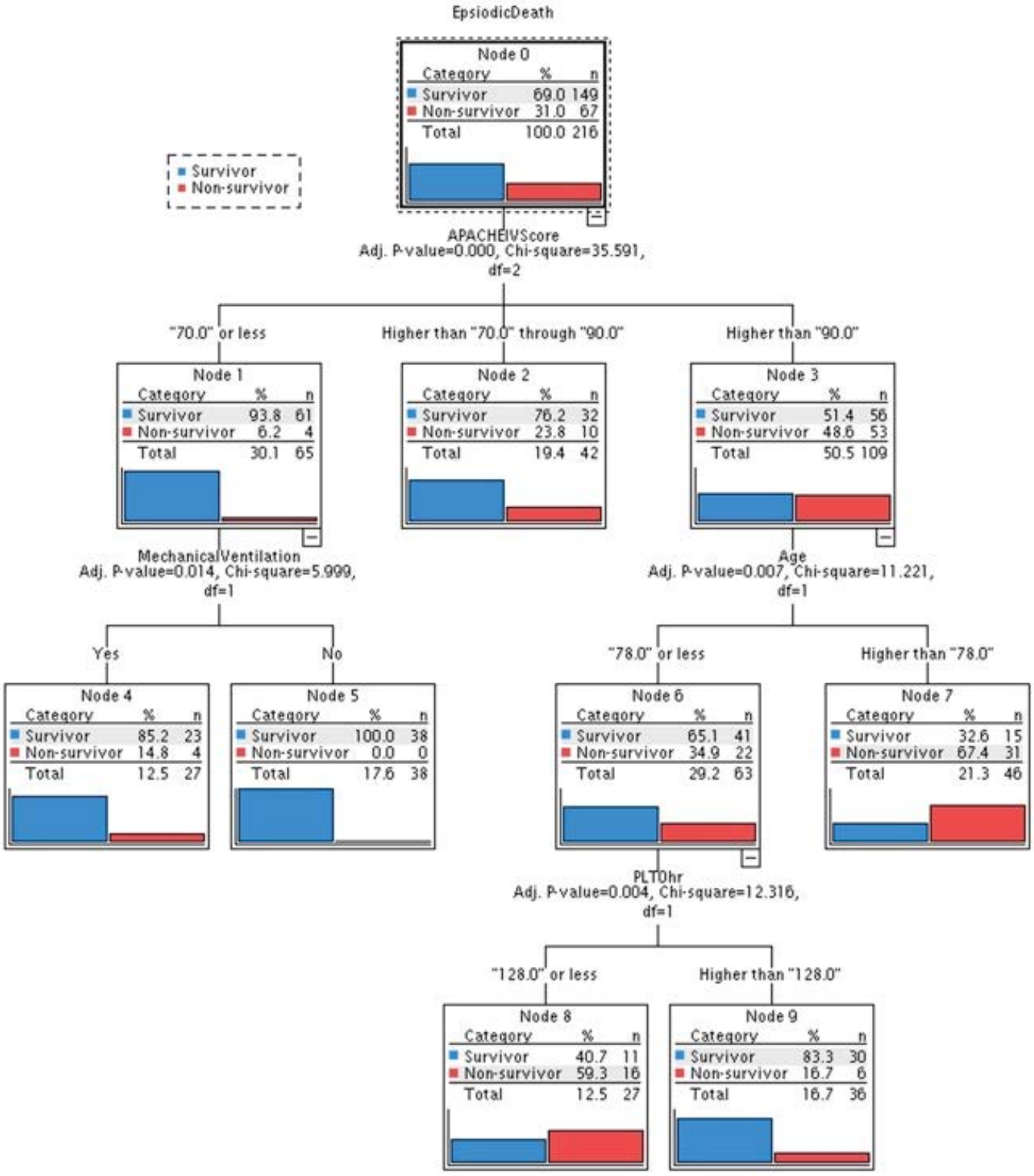

Figure 2: Classification tree analysis for predictors of hospital mortality.

WCC is not a sensitive marker even in bacteraemic patients [16]. While bandemia is more sensitive to identifying occult bacteraemia [16], the technical need for manual cell count translates to a substantial delay in diagnosis [17]. The bandemia response itself is also subject to delay and only emerges one day after clinical infection [1]. These confounding factors have led to a search for more effective markers to aid the evaluation of infections.

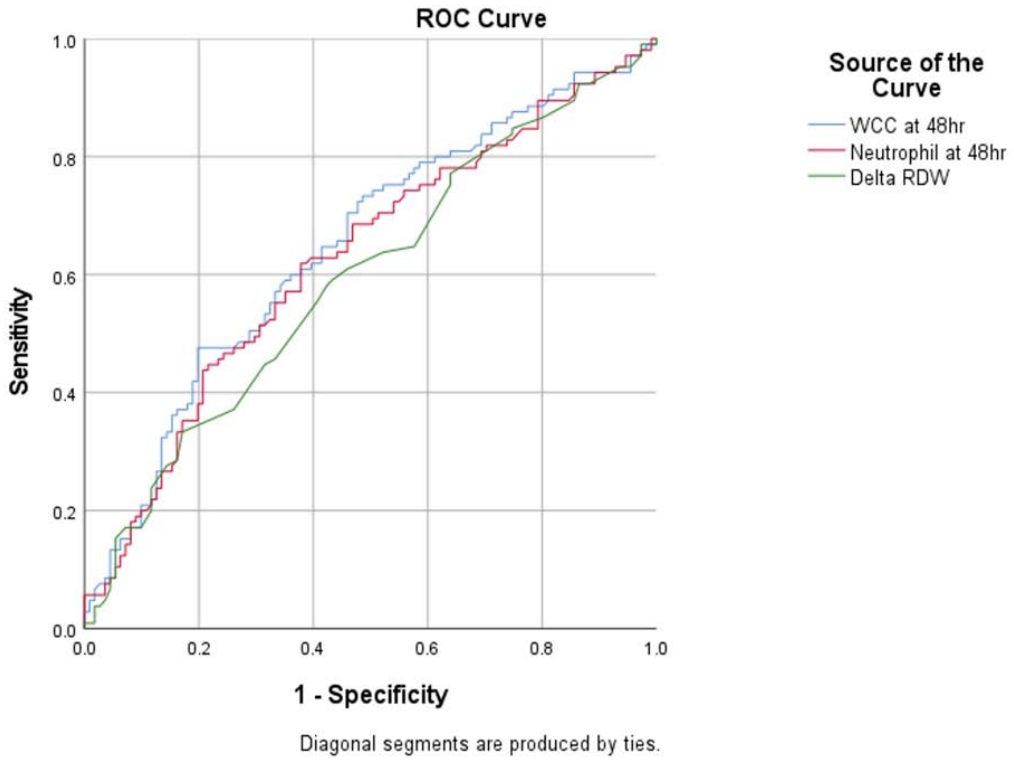

Figure 3: Receiver operating characteristic (ROC) curves to compare the diagnostic performance of laboratory parameters in differentiating viral versus bacterial pneumonia.

The neutrophil-to-lymphocyte ratio (NLR) is a readily available marker derived from the CBC as a ratio of absolute or relative neutrophil and lymphocyte counts. Endogenous catecholamines and cortisol are released in response to physiological stress, causing an increase in neutrophils and a decrease in lymphocytes [18,19]. Also, lymphocyte apoptosis occurs in sepsis leading to lymphopenia [20], resulting in an elevated NLR. This response promptly occurs within 4 to 8 hours of an acute insult [21], making the NLR superior to leukocytosis or bandemia for timely reflection of an acute illness.

NLR has been studied as a marker of severity and prognostication due to its property in identifying states of extreme physiological stress. Its use has been extensive in different fields of medicine, including rheumatic diseases [6], acute pulmonary embolism [22], acute coronary syndrome [7], and acute pancreatitis [23]. The use of NLR in predicting the severity of community-acquired pneumonia (CAP) has been intensively studied. Its performance was shown to be comparable to the pneumonia severity index (PSI) [24,25], CURB-65 [25], WCC, and CRP [25,26]. Previous studies have proven NLR to be a helpful prognostic marker for septic patients [27-29], and in general, critically ill populations (13,30,31), yet scarce literature exists on its use in the prognostication of critically ill CAP patients. To our best knowledge, our study is the first to study the use of NLR on pneumonia patients in the ICU setting. We could not demonstrate a significant difference in NLR between survivors and non-survivors in our critically ill cohort. Therefore, NLR may be a useful screening tool to stratify CAP patients before ICU admission but has limited value in prognostication of the already critically ill population.

An interesting observation from our study was the use of delta NLR in the prediction of hospital mortality. We detected a significantly higher delta NLR in non-survivors compared to survivors (3.8 vs 0.0, P=0.016), which resulted from an elevation of NLR from 0 hr (median 10.7, IQR 5.5-17.9) to 48hr (median 15.4, IQR 9.4-31.4). This persistent elevation or lack of improvement in NLR indicated treatment failure over the illness trajectory, making it a marker of poor prognosis. Our findings were consistent with previous studies that had similar observations [32,33].

Neutrophil-to-Lymphocyte ratio (NLR) in Diagnostic Differentiation of Pneumonia Aetiology

The NLR has received significant attention on its diagnostic accuracy in sepsis, pneumonia, and bacteraemia [2-5, 21,34). Several studies have proven

Table 5. Comparison of laboratory parameters between viral and bacterial pneumonia

	Total (N= 216)	Viral (N= 111)	Bacterial (N= 105)	P value
WCC				
0hr	10.7 (6.4-15.6)	9.3 (6.2-14.7)	11.8 (6.7-16.9)	0.093
48hr	11.6 (8.2-17.5)	9.9 (7.3-14.2)	13.6 (9,7-19.4)	<0.001
Delta	0.5 (-2.6-5.7)	0.6 (-1.6-3.7)	0.4 (-3.3-7.2)	0.351
Neutrophil				
0hr	9.0 (5.4-13.0)	8.1 (5.4-11.7)	9.7 (5.6-15.1)	0.084
48hr	10.3 (7.0-16.1)	8.8 (6.3-12.5)	11.6 (7.9-17.4)	0.001
Delta	0.2 (-1.5 – 4.8)	0.1 (-0.9-3.4)	0.2 (-2.3 – 6.5)	0.691
Lymphocyte				
0hr	0.7 (0.4-1.2)	0.7 (0.5-1.2)	0.7 (0.4-1.2)	0.657
48hr	0.8 (0.5-1.1)	0.7 (0.5-1.2)	0.8 (0.5-1.1)	0.486
Delta	0.0 (-0.2-0.2)	0.0 (-0.3-0.2)	0.0 (-0.2-0.3)	0.184
Monocyte				
0hr	0.4 (0.2-0.7)	0.4 (0.2-0.7)	0.3 (0.1-0.6)	0.286
48hr	0.4 (0.2-0.6)	0.4 (0.2-0.7)	0.4 (0.2-0.6)	0.456
Delta	0.0 (-0.1-0.2)	0.0 (-0.1 – 0.1)	0.0 (-0.1-0.2)	0.734
Platelet				
0hr	171 (121-224)	164 (116-212)	182 (125-235)	0.146
48hr	148 (91-197)	142 (89-188)	156 (92-207)	0.477
Delta	-21 (-54 – 6)	-17 (-47 – 7)	-26 (-57-4)	0.206
NLR				
0hr	11.6 (5.6-18.9)	11.0 (4.9 -17.2)	12.3 (7.0-21.9)	0.150
48hr	14.3 (8.0-23.7)	13.9 (6.9-20.3)	15.1 (8.7-28.1)	0.075
Delta	0.6 (-3.0 – 8.4)	0.0 (-2.3-6.7)	0.9 (-3.4-9.6)	0.517
MLR				
0hr	0.4 (0.2-0.8)	0.4 (0.2 – 0.8)	0.4 (0.2-0.9)	0.755
48hr	0.5 (0.3-0.8)	0.5 (0.3-0.9)	0.5 (0.3-0.8)	0.349
Delta	0.0 (-0.2-0.2)	0.0 (-0.2-02)	0.0 (-0.2-0.2)	0.998
RDW				
0hr	14.1 (13.3-15.4)	14.1 (13.2-15.4)	14.1 (13.4-15.4)	0.647
48hr	14.5 (13.7-15.6)	14.3 (13.6-15.5)	14.7 (13.9-15.6)	0.103
Delta	0.3 (0.0-0.6)	0.2 (-0.1-0.5)	0.3 (0.1-0.7)	0.013
PLR				
0hr	231 (132-362)	223 (128-339)	238 (134-446)	0.267
48hr	195 (120-294)	196 (119-313)	190 (124-280)	0.972
Delta	-23 (-140 – 53)	-15 (-108 – 67)	-34 (-188 – 35)	0.107

Abbreviations: WCC=white cell count; NLR=neutrophil-to-lymphocyte ratio; MLR=monocyte-lymphocyte ratio; RDW=red cell distribution width; PLR=platelet-to-lymphocyte ratio

Delta is defined by the difference between 0hr and 48 hr data (48hr minus 0hr)

Table 6. Area under receiver operating characteristic curves (AUROC) for diagnostic differentiation of viral versus bacterial pneumonia

	AUROC	SE	95% CI	HL test
WCC at 48hr	0.648	0.038	0.572-0.722	0.776
Neutrophil at 48hr	0.627	0.038	0.552-0.702	0.782
Delta RDW	0.594	0.039	0.518-0.670	0.211

HL test: Hosmer-Lemeshow goodness-of-fit test

NLR to be at least a moderate predictor of bacteraemia, with AUROCs ranging from 0.7 to 0.77(2–5). Compared to other biomarkers, including C-reactive protein (CRP) and procalcitonin (PCT), NLR showed good correlation and comparable performance in diagnosing bacterial sepsis in emergency care settings. In the critically ill population, CRP and PCT appeared to be superior to NLR in diagnosing sepsis [35-38]. However, limited literature exists on its use to determine the underlying microbiological aetiology. Our study investigated the use of NLR in discriminating between viral and bacterial pneumonia and, to our disappointment, demonstrated its inferiority compared to WCC. There were only 2 pediatric studies that investigated NLR in the differentiation of bacterial and viral pneumonia, which consistently demonstrated its poor discriminatory power [39,40]. One possible explanation could be that NLR reflects patients' physiological stress when critically ill, regardless of

the microbiological aetiology. To our best knowledge, our study was the first to investigate the use of NLR in differentiating between viral and bacterial pneumonia in the adult critically ill population.

Monocyte-to-Lymphocyte Ratio (MLR)

Monocytes are leukocytes originating from precursors in the bone marrow that are recruited to inflamed tissues via the bloodstream in response to microbial stimuli. Further differentiation into either macrophages or dendritic cells aids effective microbial clearance at infected sites [41,42]. Mobilisation of monocytes into the peripheral circulation results in an elevated MLR. MLR has been shown useful in prognostication of rheumatic diseases [43], malignancies [44], coronary artery diseases [45], stroke [46] and Guillain-Barre syndrome [47]. Recently, its use in different infections has been investigated, including cellulitis [48], respiratory virus infection [49], pneumonia [24,50,51] and bacteraemia [52].

The role of MLR as a predictor of clinical outcome has been explored in patients suffering from Klebsiella pneumonia [50]. MLR was positively correlated with mortality, and an independent predictor of severe Klebsiella pneumonia, with an AUROC of 0.888 at an optimal MLR cut-off of 0.665. We could not reproduce such a positive correlation between MLR and hospital mortality in our study. The discrepant finding may be explained by the choice of pneumococcus as the representative bacteria in our study, in contrast to Klebsiella, a gram-negative organism. The use of MLR was reviewed by Djordjevic et al. [52], who found significantly higher MLR values in patients with gram-negative blood cultures compared to gram-positive blood cultures.

The MLR can also aid in the diagnosis of bacterial and viral infections. Huang et al. reported satisfactory diagnostic performance of MLR in differentiating between patients with community-acquired pneumonia and healthy subjects [24]. Merekoulias et al. observed monocytosis, lymphopenia and hence reduced lymphocyte-to-monocyte ratio (equivalent to a raised MLR) in outpatients infected by the influenza virus during the H1N1 pandemic [49]. Subsequently, the authors proposed using the lymphocyte-to-monocyte ratio as a screening tool for influenza virus infection, especially at times where the rapid microbiologic test is in great demand.

According to the above studies, MLR may effectively discriminate patients suffering from pneumonia or infected with the influenza virus from healthy subjects. Yet, its ability to differentiate between the two types of infections is questionable. In our cohort, monocyte count, lymphocyte count and MLR were not significantly different between the viral and bacterial groups. Hence, MLR did not have significant diagnostic value in distinguishing between viral and bacterial pneumonia. To date, there is no existing literature on the use of MLR to differentiate different types of pneumonia.

Platelet (PLT) and Platelet-to-Lymphocyte Ratio (PLR)

Platelets are vital in adaptive immunity and eliciting inflammatory response besides their primary role of haemostasis [53]. A strong correlation was demonstrated between platelet count and hospital mortality in CAP patients [54-56]. Consistent with previous studies, we showed that non-survivors had significantly lower platelet counts than survivors at both 0hr and 48hr. The predictive performance of platelet count at 48hr (AUROC 0.721) was comparable to the APACHE IV score (AUROC 0.769), the best performance out of all the studied blood parameters in our study.

PLR is increasingly recognised as an indicator of the inflammatory process and is shown to have good prognostic value in patients suffering from cancers [57], acute myocardial infarction [8] or stable coronary artery disease [58]. Its use in prognostication has been extended to the critically ill and septic population, evidenced by studies showing an association between PLR and ICU length of stay [59] and even hospital mortality [60,61]. Our study was not able to demonstrate such a correlation between PLR and hospital mortality. The difference in the sample size of the cohorts may be a significant factor contributing to the inconsistent findings.

Red Cell Distribution Width (RDW)

Red cell distribution width (RDW) measures variability in red blood cell (RBC) size. Significant associations have also been demonstrated between RDW and patients with sepsis and community-acquired pneumonia [62-65]. Several mechanisms have been proposed to explain the correlation between raised RDW and inflammatory status. Pro-inflammatory cytokines such as interleukin-1β, interleukin-6, tumour necrosis factor-α are shown to shorten RBC survival [66]. Erythropoietin production and erythroid precursor cells differentiation are suppressed [67]. Compensatory release of the larger premature RBCs known as reticulocytes into the circulation results in an elevated RDW.

RDW was significantly associated with 30-day mortality when evaluated as a prognostic marker in septic patients at the emergency department [65]. Our study was able to demonstrate RDW as an independent predictor of mortality in the critically ill population. Apart from the absolute value of RDW, its change from baseline to 72 hours after admission was studied in severely septic patients attending the Emergency Department [64], and it was found to be an independent predictor of hospital mortality. Our study evaluated delta RDW, defined as the change from baseline to 48 hours after admission, and we did not reproduce the result of delta RDW as an independent predictor of mortality. However, to our surprise, delta RDW showed marginal diagnostic ability in differentiating between viral and bacterial pneumonia (AUROC 0.594). To our knowledge, there were no previous studies on the association between RDW level and aetiology of CAP.

LIMITATIONS

Our study has several limitations. Firstly, this is a single centre study, which may not be extrapolated to other centres or countries. Secondly, this is a retrospective study and potentially confounded by selection bias. Thirdly, we have chosen Streptococcus pneumoniae as a representative organism for bacterial pneumonia and influenza A for viral pneumonia. Our results may not represent bacterial and viral pneumonia caused by organisms other than pneumococcus and influenza A. Fourthly, we have not included novel biomarkers like C-reactive protein (CRP) and procalcitonin (PCT), which have been extensively studied and found helpful in prognostication in critically ill septic patients. These markers were not readily available in our hospital at the start of our study period and hence could not be incorporated to compare the studied biomarkers. Lastly, we have not excluded patients with an immunocompromised state, for instance, patients on long term corticosteroid use and those infected with human immunodeficiency virus (HIV). These factors can significantly impact the baseline neutrophil count and, hence, the neutrophil-to-lymphocyte ratio, causing confounding in the interpretation of these biomarkers. Also, we have included patients with active haematological malignancies (5.6%) in our study. The use of NLR has not been validated in this population, and cautious interpretation must be exercised.

CONCLUSIONS

In predicting the outcome of critically ill CAP patients, the prognostic power of the APACHE IV score remains superior to all the studied blood parameters. The addition of other factors that are independent predictors of mortality to the APACHE IV score further strengthens its prognostic power. However, the APACHE IV score is limited by the need for multiple clinical and laboratory parameters, which is deemed less convenient than parameters directly derived from a simple complete blood count. In our cohort, the single, simple biomarker with comparable prognostic performance to the APACHE IV score by the ROC analysis is platelet count at 48 hrs. Further studies may be carried out to investigate the use of other novel inflammatory markers such as CRP and PCT in the critically ill pneumonia population. The use of multiple, composite biomarkers inclusive of CRP and PCT, instead of single biomarkers, can also be considered and compared with the predictive power of the APACHE IV score.

In determining the aetiology of pneumonia in critically ill patients, no single biomarker has good diagnostic accuracy.

ETHICAL STATEMENT

This study was approved by the Hong Kong East Cluster Ethics Committee of the Hospital Authority (HKECREC-2020-071). Written informed consent was waived.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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