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Diagnostic value of biomarkers for sepsis in adult patients in the emergency department: Don't forget the neutrophil-lymphocyte count ratio

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ABSTRACT

Objective: To determine and compare the diagnostic efficiency of various biomarkers [C-reactive protein, neutrophil percentage, neutrophil-lymphocyte ratio (NLCR), lactate, procalcitonin, blood culture] in the identification of septic patients in emergency department (ED), and to assess the predictive value of combination of markers. **Methods:** This was a prospective, single centre study conducted in the ED of an urban, tertiary care hospital. We included patients who were admitted to the ED with symptoms of a possible infection. Blood cultures and serum measurement of the biomarkers were collected from 131 patients. Patients were determined to be septic or non-septic, based on the systemic inflammatory response syndrome criteria and the diagnosis was made at the ED. Sensitivity, specificity, positive predictive value, negative predictive value and area under curves (AUC) were calculated. **Results:** A total of 126 patients, 61 with sepsis and 65 without sepsis were eventually included in the study. Neutrophil to lymphocyte ratio displayed the highest accuracy in diagnosing sepsis (AUC 0.735, 95% CI=0.648-0.822, $P<0.001$). The best combination of markers in predicting sepsis was NLCR and white blood cell (AUC: 0.801, 95% CI=0.724-0.878, $P<0.001$). **Conclusions:** The results of this small study showed that NLCR outperforms other markers in diagnosing sepsis in ED. It is readily available, cost efficient, non invasive and independent. It may be insufficient to rely on this single marker to diagnose sepsis, so some other diagnostic utilities should be taken into account as one part of the overall assessment. Our study also showed that combination of NLCR and white blood cell provides the highest diagnostic accuracy. More large scale studies across different population groups will be needed to confirm this finding.

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1. Introduction

The diagnosis of sepsis remains a challenge for front line clinicians. According to the International Surviving Sepsis Campaign, early diagnosis and management of sepsis are essential in reducing mortality[1]. However, sepsis is especially difficult to diagnose in emergency department (ED), where many of these patients often present in an undifferentiated, atypical manner. The documentation of infection can be made with a positive blood culture[2]. However, blood cultures are typically not available until 12 h to 48 h later. This has led to the development and evaluation of various inflammatory and infective markers as a earlier predictor of sepsis[1,3-14].

Traditional markers of infection and inflammation such as C-reactive protein (CRP) and white blood cell (WBC) count have been evaluated for their diagnostic ability to predict sepsis extensively[14-17]. Recently, newer markers such as neutrophil-lymphocyte ratio (NLCR) are also shown to be useful in predicting bacteremia in ED[4]. However, the usefulness of NLCR as a marker to predict sepsis, especially in Asian context, needs further exploration. It may be less reliable to use individual marker to diagnose sepsis, so combination of various markers may be more effective in aiding diagnosis as shown in some studies[17-23].

The aim of this prospective study is to determine and compare the diagnostic efficiency of various biomarkers [CRP, neutrophil percentage, WBC, NLCR, lactate, procalcitonin (PCT), blood culture] in identification of septic patients in ED and to determine which combination of markers has the best predictive value.

2. Materials and methods

2.1. Recruitment

This study has institution IRB's approval: CIRB 2014/657/C, Doc Number 205-001. A total of 131 adult patients with complaints suggestive of an infection were recruited. Patients with the followings were excluded: age below 21 years; known pregnancy; prisoners; Do-Not-Resuscitate status; primary diagnosis of trauma, burns, active seizure, acute cerebral vascular accident, acute coronary syndrome, status asthmaticus, major cardiac arrhythmias, active gastrointestinal haemorrhage, drug overdose; requirement for immediate surgery; active chemotherapy; haematological malignancy; inability to provide informed consent and comply with study requirements. There was no conflict of interest in conducting this study.

Upon arrival to the ED, each participant was triaged by a nurse and their vital signs were measured (temperature obtained by a tympanic thermometer; blood pressure, heart rate and oxygen and respiratory rate). Thereafter, clinical history was taken and physical examinations were performed by an ED doctor. A total of 12 mL of blood was drawn once for all recruited participants. Appropriate

blood and radiological investigations were ordered as part of routine care. Of these investigations, the following were ordered for all participants: full blood count, lactate, PCT, CRP and one set of aerobic and anaerobic blood cultures. After the appropriate investigations, a diagnosis was then assigned to each participant by the ED doctors.

The participants of the study were stratified into two groups, including septic group and non-septic group, based on the systemic inflammatory response syndrome (SIRS) criteria and the diagnoses given at the ED. SIRS was defined, as the participants fulfilled at least two of the following four criteria: Temperature $<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$; Respiratory rate >20 breaths per minute or $\text{PaCO}_2 <32$ mmHg; Heart rate >90 beats per minute and WBC $<4\ 000/\text{mm}^3$ or $>12\ 000/\text{mm}^3$ or the presence of immature neutrophils $>10\%$ [5,8,10]. Patients in the septic group were those who fulfilled the SIRS criteria at presentation and had an diagnosis of infection. Patients in the non-septic group included; (1) Patients who fulfilled SIRS criteria at presentation but did not have a diagnosis of infection; (2) Patients who had a diagnosis of infection, but did not fulfill the SIRS criteria at presentation and (3) Patients who neither fulfilled SIRS criteria at presentation nor had a diagnosis of infection.

We decided to use the SIRS criteria instead of the Sequential (sepsis-related) Organ Failure Assessment, as it has been widely validated previously. Moreover, it had been used in our ED for some years[3,6-10].

2.2. Statistical analysis

Statistical analysis was carried out by using IBM® SPSS® Statistics Version 24.0. All statistical comparisons were two-tailed, and a *P* value of less than 0.05 was regarded as statistically significant difference.

Firstly, the sensitivity, specificity, positive predictive value and negative predictive value for each marker based on the lab cut-offs were analyzed using the standard method for deriving these values. Then, an independent *t*-test was carried out to look for significant differences in the mean values of the continuous variables (CRP, PCT, lactate, NLCR, neutrophil percentage and age) between the septic and non-septic group. *Chi*-squared tests and Fisher's exact test was carried out for nominal variables (WBC, blood culture, gender and race). Variables with a significant association with sepsis were included for receiver operating characteristics (ROC) curve to assess their combined predictive value of sepsis as shown by the area under curve (AUC).

Individual ROC curve of each marker was constructed and AUCs were compared to determine the marker with the best diagnostic accuracy. ROC curves of different combinations of markers which showed significant association with sepsis were also generated. Then AUCs were compared to determine which combination of markers was the best predictive indicator of sepsis. Youden's index was calculated for the individual ROC curve to identify the cut-off

that maximizes the sensitivity and specificity of each marker. The positive predictive and negative predictive values of each marker were then calculated based on these cut-offs.

3. Results

A total of 131 participants [mean age: (66±19) years, age range: 23-98 years] were enrolled in the study. Five participants were excluded from the analysis as some data for the stratification of patients into sepsis and non-sepsis groups were lacking. Hence, 126 participants [mean age: (66±19) years, age range: 23-98 years] were further analyzed in this study. Of the 126 participants, 2 participants were excluded in the analysis involving CRP, 13 involving lactate and 1 involving PCT as lab values for these markers were lacking.

The septic group had 61 patients [mean age: (62±19) years, age range: 23-97 years] while the non-septic group had 65 patients [mean age: (70±19) years, age range: 25-98 years]. The septic group was made up of 29 females and 32 males while the non-septic group was made up of 31 females and 34 males. There was significant difference in age between the 2 groups ($P=0.014$) while race and gender showed no significant association with sepsis ($P>0.05$).

The means of various sepsis markers were then compared between the septic and non-septic group. Significant differences in the CRP levels, neutrophil percentage and NLCR between the septic and non-septic groups were found (Table 1) ($P<0.05$). An abnormal WBC was also found to be associated with sepsis ($P<0.001$). WBC was assessed as a nominal variable to account for the upper and lower limit cut offs in the SIRS criteria. This means that WBC would be assessed as “within the normal range” (ie 4-12) or “not within the normal range” (ie <4 or >12). This is also why there is no mean value designated for WBC in Table 1. The mean values of lactate and PCT in the septic group did not significantly differ from that in the non-septic group ($P>0.05$). A positive blood culture was also not found to be associated with sepsis ($P>0.05$).

Table 3

Characteristics of each marker at lab cut-off versus cut-off determined by the Youden's index.

Sepsis marker	Cut-offs	Sensitivity	Specificity	Positive predictive value	Negative predictive value
C-reactive protein	Lab cut off: 0.2-9.1 mg/L	0.934 (0.833-0.979)	0.206 (0.119-0.330)	0.533 (0.434-0.629)	0.765 (0.498-0.922)
	Cut-off that maximises AUC: <23.3 mg/L	0.820 (0.722-0.918)	0.429 (0.331-0.527)	0.581 (0.483-0.679)	0.711 (0.613-0.809)
PCT	Lab cut off: <0.5 ng/mL	0.475 (0.379-0.571)	0.703 (0.607-0.799)	0.604 (0.508-0.700)	0.584 (0.488-0.680)
	Cut-off that maximises AUC: <0.195 ng/mL	0.754 (0.658-0.850)	0.516 (0.420-0.612)	0.597 (0.501-0.693)	0.688 (0.592-0.784)
Neutrophil percentage	Lab cut off: 40%-75%	0.803 (0.705-0.901)	0.446 (0.348-0.544)	0.576 (0.478-0.674)	0.707 (0.609-0.805)
	Cut-off that maximises AUC: $<85.7\%$	0.508 (0.410-0.606)	0.800 (0.702-0.898)	0.705 (0.607-0.803)	0.634 (0.536-0.732)
NLCR	Lab cut off: $</=10$	0.607 (0.509-0.705)	0.708 (0.610-0.806)	0.661 (0.563-0.759)	0.657 (0.559-0.755)
	Cut-off that maximises AUC: <8.6	0.656 (0.558-0.754)	0.662 (0.564-0.760)	0.645 (0.547-0.743)	0.672 (0.574-0.770)
Lactate	Lab cut off: 0.5-2.2 mmol/L	0.345 (0.239-0.451)	0.745 (0.639-0.851)	0.588 (0.482-0.694)	0.519 (0.413-0.625)
	Cut-off that maximises AUC: <1.5 mmol/L	0.672 (0.566-0.778)	0.472 (0.366-0.578)	0.582 (0.476-0.688)	0.586 (0.480-0.692)
WBC	Lab cut off: 4.0-12.0 cells/mm ³	0.820 (0.696-0.902)	0.615 (0.486-0.731)	0.667 (0.547-0.769)	0.333 (0.231-0.453)

Data expressed in brackets represent the 95% confidence interval.

Table 1

Sepsis markers in septic and non-septic group.

Sepsis markers	Septic group	Non-septic group	P-value
CRP (mg/L)	134.8±123.1	91.8±109.6	0.042
Neutrophil percentage (%)	803.2±138.6	750.5±118.8	0.023
NLCR	144.0±139.7	80.1±64.8	0.002
Lactate (mmol/L)	2.1±1.2	1.9±1.0	0.212
PCT (μ g/L)	455.2±1 257.0	198.7±632.1	0.156

Data is expressed as mean ± standard deviation.

For values in Table 1, some of the standard deviation (SD) values are noted to be quite close to, equal or even higher than the mean values. The reasons for this are likely:

- (1)The SD is always a positive value, but the mean can be zero;
- (2)A higher SD than the mean can be due to the data set being very widely distributed, with a stronger positive skewness;
- (3)Both the SD and the mean are metrics of different measurements, and although the SD is used as a unit measurement on a normal distribution, this may not be its sole function. It is a general measure of spread. The mean, on the other hand, is a measure of location.

ROC curve analysis for each markers was carried out and the AUCs are shown in Table 2. Age was also included in the construction of the ROC curve as it was found to be a possible confounder for the relationship between NLCR and sepsis as well as WBC and sepsis, when analyzed using binomial regression. NLCR was noted to have the highest AUC 0.735 (95% $CI=0.648-0.822$, $P<0.001$). The AUC for lactate was the lowest at 0.557 (95% $CI=0.450-0.663$) and the result was noted to be insignificant ($P>0.05$). The cut-off value that maximised the sensitivity and specificity was obtained for each sepsis marker using the Youden's index. The sensitivity, specificity, positive predictive value and negative predictive value of all the markers were calculated for this cut-off and the lab cut-offs are shown in Table 3. In Table 3 also, because we utilized WBC as a nominal variable, the ROC curve was not created and thus, we did not derive a new cut off for WBC.

Table 2

AUC and cut-off for Individual ROC.

Sepsis marker	AUC	95% CI	P-value	Cut off that maximises AUC
NLCR	0.735	0.648-0.822	<0.001	8.6
Neutrophil percentage	0.664	0.566-0.761	0.002	85.7%
PCT	0.652	0.556-0.748	0.003	0.195 µg/L
CRP	0.631	0.533-0.729	0.012	23.3 mg/L
Lactate	0.557	0.450-0.663	0.300	1.55 mmol/L

Based on the results of the independent *t*-test, 5 variables (CRP, neutrophil percentage, NLCR, age and WBC) were analyzed to assess their discriminatory ability in diagnosis of sepsis. This produced an AUC of 0.792 (95% CI=0.713-0.871) (*P*<0.001) (Figure 1). The AUC of the various combinations of 2 sepsis markers are summarized in Table 4. The AUC of the various combinations of 3 sepsis markers are summarized in Table 5. The highest AUC, 0.801 (95% CI=0.724-0.878, *P*<0.001) was obtained by combining NLCR and WBC (Figure 2).

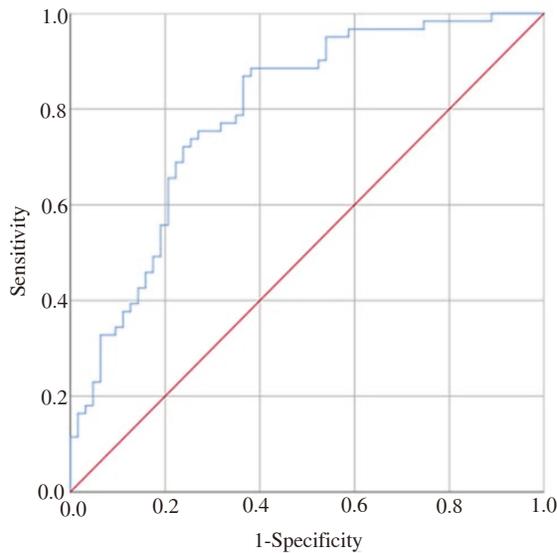


Figure 1. Fully combined ROC curve (CRP, NLCR, neutrophil percentage, WBC).

Table 4

ROC for combination of 2 markers.

Sepsis markers	AUC	95% CI	P-value
NLCR, CRP	0.743	0.656-0.830	0.045
NLC, neutrophil percentage	0.738	0.651-0.825	0.044
CRP, neutrophil percentage	0.647	0.549-0.744	0.050
NLCR, WBC	0.801	0.724-0.878	<0.001
WBC, CRP	0.769	0.685-0.853	<0.001
WBC, neutrophil percentage	0.787	0.707-0.866	<0.001

Table 5

ROC for combination of 3 markers.

Sepsis markers	AUC	95% CI	P-value
NLCR, CRP, neutrophil percentage	0.745	0.658-0.832	<0.001
NLCR, CRP, WBC	0.794	0.715-0.873	<0.001
NLCR, WBC, neutrophil percentage	0.793	0.716-0.871	<0.001
CRP, WBC, neutrophil percentage	0.776	0.693-0.859	<0.001

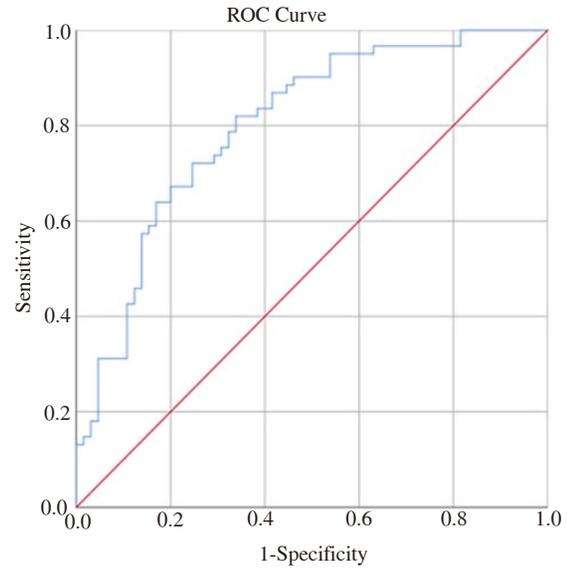


Figure 2. Best 2-marker combined ROC (NLCR and WBC).

4. Discussion

Sepsis is a systemic disease with variable clinical presentations, but there is a gold standard for a definite diagnosis. SIRS was one of the earlier criteria used to assist practitioners in the diagnosis of the spectrum of sepsis. The latest, the Third International Consensus Definitions for Sepsis and Septic Shock proposed an update and revision of the definition and clinical criteria for sepsis (Sepsis-3)[1,3,5,10]. Despite many publications on these criteria, the results seem to vary according to factors such as patient cohort, time of recruitment and diagnosis, amongst other variables. However, early identification and initiation of therapy is essential in decreasing mortality associated with sepsis (early goal directed therapy). In this study, we evaluated the predictive value of some of available biomarkers in order to aid in early diagnosis of sepsis in ED setting[14,18,21].

4.1. Blood culture

In general, sepsis is exemplified by bacteremia and its consequences. The inflammatory response is stimulated by the endotoxins that the bacteria produce, as virulence factors. When sepsis progresses (to septic shock), there will be further significant dysregulation of pro- and anti-inflammatory cycles of cytokines and other regulatory molecules. Blood cultures can detect markers

of pathogens in the laboratory. However, this method is less viable as a front line diagnostic tool, for the outcomes can be unpredictable and may take too much time. Even as guidelines recommend two sets of blood cultures, this must be balanced with the severity of illness and presentation of the patients, and should not cause a significant delay in the administration of antimicrobials and other necessary treatment[11].

In this study, out of the 126 participants, 61 participants were classified into the septic group based on SIRS criteria and the presence of a diagnosis of infection given at the ED. However, only 4 participants (6.6%) in the septic group were noted to have a positive blood culture. Furthermore, 6 out of the 65 non-septic participants (9.2%) also had a positive blood culture. Although a positive blood culture is often seen as an ideal method of diagnosing sepsis[2,15], our study results showed poor correlation between positive blood culture and sepsis. Other studies showed similar results with the percentage of true positive blood cultures being about 10%[16-18]. A study evaluating the usefulness of blood cultures in aiding management in ED showed only 6.4% of the blood cultures were true positive and suggested eliminating the routine usage of blood cultures in immunocompetent patients with common illnesses such as urinary tract infection, community acquired pneumonia and cellulitis[18]. However, a study of Hoenigl *et al.* reported that 41.6% of patients who fulfilled the SIRS criteria, had a positive blood culture[20]. This increased percentage of true positive blood cultures may be attributed to the fact that this study evaluated the blood cultures based on 3 sets of blood cultures compared to our study which only did 1 set of blood cultures.

4.2. PCT

In our study, it is shown that PCT was a relatively good marker in diagnosing sepsis, as it had an AUC of 0.652. This finding is similar to many other studies whereby PCT was found to be a valuable marker in diagnosing either sepsis or bacteremia in ED, where its AUC ranged from 0.69 to 0.79 in these studies[21-23]. A possible reason that can explain the lower diagnostic accuracy is that our study had a small sample size. Referencing results from a study done by Ugarte *et al.*[24] that used a similar PCT cut off of 0.6 ng/mL, and our results for positive predictive value and negative predictive value are comparable. That study's results obtained a sensitivity of 67.6%, specificity of 61.3%, positive predictive value of 71.0% and negative predictive value of 57.5%. The difference in patient populations (ICU *vs.* ED) could explain the lower specificity obtained in their study (61.3% *vs.* 70.3%), as ICU patients may have a higher baseline of PCT value. Several factors can contribute to such a result[23,24]. Firstly, for ICU patients, PCT may be raised for up to several weeks after infection onset and these patients may have had multiple episodes of bacterial infection during their ICU stay. Also, many conditions associated with ICU care (profound circulatory failure, major surgery, trauma, pancreatitis, *etc.*) trigger systemic release of inflammatory mediators responsible for non-specific PCT increase.

4.3. CRP

In our study, CRP produced an AUC of 0.631 that was lesser than that produced by PCT, neutrophil percentage and NLCR. This result is comparable to other studies. A study done on ED patients with suspected community-acquired bacteraemia showed that CRP produced an AUC of 0.62 (*CI*=0.54 to 0.70)[4]. This study also reported a sensitivity of 75.0%, specificity of 37.0%, positive predictive value of 54.3%, and negative predictive value of 59.6%. Compared to this study, our results showed greater sensitivity and negative predictive value but lower specificity and positive predictive value. This is in line with the usage of CRP as a sensitive marker for infection but not a specific marker especially in the presence of other inflammatory conditions[25]. The higher sensitivity and negative predictive value achieved in our study might be explained by the the much lower cut-off used for our study compared to that study (0.2 mg/L-9.1 mg/L *vs.* >50 mg/L). With a lower cut off value, we were able to achieve a higher negative predictive value. However, the sensitivity of 93.4% seen in our study may be too low for it to be used as a test to rule out sepsis. This sensitivity and specificity provides a negative likelihood ratio of 0.32 showing that it has limited clinical utility for such usage. Another aspect that could have been further explored would be the effect of participants' comorbidities such as hepatic disease or immunosuppression and duration of illness on the utility of CRP in diagnosing or ruling out sepsis in ED[26].

4.4. WBC

Although infected patients had WBC counts that statistically differed from those of uninfected patients in this investigation, many other studies have found no such difference[4,27-31]. This is presumably due to different characteristics of the patient populations studied. The present investigation included a broad range of unselected medical patients in ED, based on our recruitment definition, compared to the other studies.

4.5. Neutrophil percentage

Neutrophil percentage has not been given much focus, and thus it was not well studied as a marker of sepsis or infection. Results from a study found that neutrophil percentage may be a good marker in predicting sepsis in patients with chronic kidney disease[30]. Another study showed that it is a poor marker of bloodstream infections in burns patients[31]. Despite this, our study has shown that neutrophil percentage is a moderately good marker in predicting sepsis in ED, given its AUC of 0.664. With regard to the lack of studies investigating the value of neutrophil percentage as an early marker of sepsis in the ED, more studies are needed to confirm the results from our study.

4.6. Lactate

Many studies have investigated the prognostic value of lactate in sepsis and have concluded that lactate has a good ability to predict mortality in septic patients[19,25,32,33]. However, few studies investigate the diagnostic power of lactate in predicting sepsis in ED patients. One such study[33] that investigated the diagnostic utility of lactate amongst other markers in predicting bacteremia in ED found that lactate has an AUC of 0.69 at an optimal cut-off of 17.9 mg/dL while our study obtained an AUC of 0.557 at an optimal cut-off of 0.994 mmol/L.

4.7. NLCR

The use of NLCR as an indicator of severity of infection has been proposed by several studies[34-38]. This utilizes the physiological mechanism in which neutrophil levels rise and lymphocyte levels fall in response to stressful events. Lymphopenia has been described as a marker of bacteremia, but may not have garnered a strong enough traction as a marker for infection. In the blood of septic patients, lymphocyte apoptosis is increased, which leads to persistent or prolonged lymphopenia[37-42]. NLCR is also gaining more interest as a useful predictor of survival and also as an independent, low cost marker, which is readily available[37,41]. In fact NLCR is available from full blood count, which most patients with the presentation of the sepsis and SIRS syndrome will have as a routine investigation.

In our study, NLCR was evaluated with age that was noted to be a possible confounder for the relationship between NLCR and sepsis. The AUC of the ROC curve produced by NLCR and age against sepsis is 0.735 [95% CI=0.648-0.822, ($P<0.001$)]. This result is comparable to other studies that also reported an AUC ranging from 0.720-0.770[34,36,38,40,41]. NLCR, as noted previously, had the highest AUC attained by a single marker in our study. This is corroborated by studies which also showed that NLCR had a greater AUC compared to CRP and WBC[34,38, 40,41]. Another factor to consider is the cut-off for the NLCR. There are only few studies that have set out to address this categorically, and from the other publications on the topic, the range is between 5 to 10[4,36,38,42].

4.8. Other markers

Besides the markers addressed in this paper, there are others shared in smaller and fewer studies as well as publications[43-45]. Djordjevic *et al* discussed the use of the other ratios besides NLCR; namely the monocyte to lymphocyte and the platelet to lymphocyte ratios and their links to poor patient outcomes[44]. The values for these ratios are readily available from full blood count, thus making them relatively low cost as well. Other markers like interleukin-6 and soluble triggering receptor expression myeloid cells are also gaining traction.

There have also been more interests in the gene expression in

sepsis and SIRS[45,46]. Sweeney *et al.*, for example has indicated 11 genes that robustly distinguish sterile inflammation from infection inflammation[45]. These may allow for the earlier confirmation of the patient groups that may have more serious outcomes. Many have also stated that even with these investigations available, a lot still depend on the clinical situation and manifestations.

4.9. Limitations

As with all studies, ours has some limitations. Firstly, we conducted this study based on participants from a single centre. Our total population numbers were limited given the limited recruitment period and location. It would have been better if we conducted the study on a larger local population to accurately assess the trends in our context. Furthermore, many of the sepsis markers are all part of a physiological response to stress, and we did not fully evaluate other factors that could affect these levels. Some of such factors that could be analyzed in the future would be co-morbidities, duration of illness and recent antibiotic usage, to name a few. Lastly, although we aimed to find the best combination of factors that would aid in the diagnosis of sepsis, we did not consider factors such as the cost of the panel and turn around time that may play a part in clinical decision making. We focused on markers that were usually ordered routinely, and hence we believe that eventually adopting a specific combination of markers to look at should decrease the cost if at all.

4.10. Conclusion

To be concluded, based on our study results, NLCR is the best individual marker that helps to predict sepsis in our study population. NLCR is an easily available value, and can be gleaned from full blood count that is almost always ordered as part of routine care. More studies are needed to look into this relatively new and promising marker. In terms of more than 1 marker, the best combination based on our results will be that of NLCR and WBC. An area of further study in this field would be to further assess the role of age in the relationship of these markers with sepsis. This combination notably produced an AUC that is greater than that with all the significant markers combined and is hence the most effective combination identified in our study. Further studies with larger population are needed in this field and such studies can guide us towards a concrete recommendation on how to identify sepsis in ED.

Conflict of interest statement

The authors report no conflict of interest.

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