UTILITY OF HAEMOGRAM PARAMETERS IN MORTALITY RISK PREDICTION OF CRITICALLY ILL PATIENTS

Poongodi Rajagopal¹, Sudhakar Ramamoorthy², Angelin Grace Jeslin³

¹Assistant Professor, Department of Pathology, Velammal Medical College Hospital and Research Institute.

²Assistant Professor, Department of Pathology, Velammal Medical College Hospital and Research Institute.

³Undergraduate Student, Velammal Medical College Hospital and Research Institute.

ABSTRACT

BACKGROUND

Mortality risk prediction using varying factors is an emerging tool in medicine. Factors which predict mortality can help clinicians to triage the patients, modify the treatment accordingly and give special care to the patients. Different studies have used different parameters in different disease settings to predict mortality risk, evolving from simple blood counts to many sophisticated techniques. Although several of those clinical scores are available, they are found to be too complex for clinical use. Hence identifying a simple tool becomes essential.

MATERIALS AND METHODS

The study was performed in a tertiary care hospital. The study was a retrospective analysis of 100 patients who were admitted and expired in intensive care units. For comparison, 100 age and sex matched patients who had been admitted in ICU and recovered from the illness were taken as controls. Twelve haematological parameters have been analysed in both study and control groups. Parameters that proved significantly different between the groups were identified and cut off derived using Receiver operating characteristic analysis. Binary logistic regression models were also plotted to identify additional parameters that were significant.

RESULTS

Of twelve haematological parameters analysed, significant differences were identified in RDW, TLC, ANC and neutrophil-lymphocyte ratio by univariate analysis. Patients with cut-off values RDW $\geq 14.65\%$, TLC $\geq 12000/\text{cumm}$, ANC $\geq 9156/\text{cumm}$ and NLR ≥ 5 can predict mortality in critically ill patients with sensitivity varies from 66% to 80%.

CONCLUSION

Basic haematological parameters can be used as a simple and cost-effective tool to predict mortality and to provide early treatment in critically ill patients.

KEYWORDS

Critically Ill, Mortality, Red Cell Distribution Width, Blood Cell Count, NLR.

HOW TO CITE THIS ARTICLE: Rajagopal P, Ramamoorthy S, Jeslin AG. Utility of haemogram parameters in mortality risk prediction of critically ill patients. J. Evolution Med. Dent. Sci. 2018;7(08):1024-1029, DOI: 10.14260/jemds/2018/234

BACKGROUND

Death is usually associated with the process of loss of organ function accompanied by stress responses and complex reactions in the body. Studies showed that these physiological changes could influence the haematological and biochemical parameters during the period of terminal illness.¹ Mortality risk prediction in critically ill patients has evolved from simple counts to more sophisticated techniques. For example, in intensive care unit (ICU) settings, clinical based prognostic scores are more often used such as Acute Physiology And Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Score (SOFA) than diagnosis-based scoring systems.²

However, they are yet considered too complex for clinical use. So, there is a need to identify simpler prognostic tools which can help in mortality risk stratification. There have been various studies in this field which have demonstrated some of the haematological parameters like red cell distribution width (RDW), ANC, ALC, platelet count and derived parameters like NLR, LMR and PLR as predictors of mortality. One of the most studied prognostic marker is NLR. Various studies have shown the valuable role of NLR in predicting postoperative patient outcome, overall survival, cancer disease-free survival and patient's sensitiveness to specific chemotherapy.^{3, 4, 5} NLR has also been shown to be associated with adverse events in stable coronary disease, long-term mortality in patients with ST-segment elevation myocardial infarction (STEMI), in-hospital and six-month mortality in acute coronary syndrome.^{6,7}

In the study done by Riche et al, it was observed that according to the timing of death of septic shock patients NLR ratio varied. Early death had a low NLR at admission in contrast to an increased NLR during the first 5 days in cases of late deaths.⁸ Reactive increase in platelet count was found to be associated with lower survival after surgery for several types of cancer due to raised IL-6 which triggers megakaryocyte differentiation in these cases.⁹ Association between high NLR and platelet count in gastric cancer prognosis was reported by Shimada et al.¹⁰ PLR, a marker

'Financial or Other Competing Interest': None.
Submission 25-01-2018, Peer Review 10-02-2018,
Acceptance 13-02-2018, Published 19-02-2018.

Corresponding Author:
Sudhakar Ramamoorthy,
Assistant Professor,
Department of Pathology,
Velammal Medical College
Hospital and Research Institute,
Anuppanadi, Madurai-625009.
E-mail: dr.sudhakar2k3@gmail.com
DOI: 10.14260/jemds/2018/234

related to platelet proliferation has been identified as a prognostic marker in patients with advanced gastric cancer treated with chemotherapy. PLR has helped in identifying more sensitive patients to specific chemotherapy. Recently work done by Shao et al using biomarkers of systemic inflammation including the Glasgow Prognostic Score (GPS), modified GPS (mGPS), C-Reactive Protein Albumin (CRP/Alb) ratio, NLR, PLR and LMR have shown that these biomarkers have emerged as prognostic factors in oesophageal cancers.¹¹ Among red cell indices, higher RDW is associated with increased risk of mortality in haemodialysis, coronary artery disease, heart failure, septic shock, pulmonary embolism and in cancer patients.^{12, 13} Study done by Kho et al was the first one to include almost all the CBC variables and they have reported that the presence of nucleated RBCs, burr cells, and absolute lymphocytosis at admission were independently associated with a 3-fold increase in risk of death within 30 days of admission. However, this study had not taken derived parameters like NLR, LMR and PLR.¹⁴ Since then, very few studies have evaluated complete haemogram parameters as a predictor of mortality in critically ill patients.

Since mortality predictors are very much needed especially in ICU settings where the patients are critically ill, identifying a simple, cost effective, reproducible and reliable tool becomes necessary for the clinicians to triage and plan treatment accordingly. In view of this, we sought to evaluate 12 haematological parameters to derive a simple and effective prognostic tool to predict mortality in critically ill patients.

Aims & Objectives

To identify the haematology parameters which can predict mortality in critically ill patients

MATERIALS AND METHODS

The study was a retrospective analysis of 100 mortality cases who were admitted in intensive care units of our tertiary care hospital. Cases where haemogram reports available for the last 48 hours were included in the study. For comparison, 100 age and sex matched patients who had been admitted in ICU and recovered from the critical illness were taken as controls. Case files and complete blood count reports of both cases and controls were retrieved. Complete blood count analysis is being carried out in our hospital using Beckman Coluter LH750 automated haematology analyser. Following parameters were noted from the complete blood count reports-

1. Haemoglobin (Hb)
2. RBC count.
3. Red cell distribution width (RDW)
4. Total leucocyte count (TLC)
5. Absolute neutrophil count (ANC)
6. Absolute lymphocyte count (ALC)
7. Absolute monocyte count (AMC)
8. Platelet count.
9. Mean platelet volume (MPV)
10. Neutrophil-lymphocyte ratio (NLR)
11. Lymphocyte-monocyte ratio (LMR)
12. Platelet-lymphocyte ratio (PLR)

Out of these 12 parameters, the first nine were direct parameters measured by automated haematology analyser. The last three were calculated parameters where NLR is the ratio of absolute neutrophil count and absolute lymphocyte count, LMR is the ratio of absolute lymphocyte count and absolute monocyte count and PLR is the ratio of platelet count and absolute lymphocyte count.

Exclusion criteria

1. All paediatric cases were excluded from the study as reference ranges of various parameters differ between children and adults.
2. Patients admitted in ICU due to non-pathological conditions (E.g.: Trauma, burns) were excluded from the study.
3. All primary bone marrow diseases which would directly influence the haemogram values as a part of disease process were excluded from the study.

Statistical Analysis

Data collected were entered into Microsoft Excel program and analysis was carried out using Statistical Package for Social Sciences (SPSS) version 22. Descriptive analysis was done for all variables included in the study. Frequencies and proportions were given for categorical variables and mean and standard deviation were provided for continuous variables. Inferential statistics were also calculated for comparison of various study parameters across subgroups using statistical tests. The means of various haematological parameters (such as Hb, RBC, RDW and others) were compared between cases and controls by student's t test. Association between anaemia grading and case-control status was tested by Chi-square statistics. Mean differences in haematological parameters across case and control groups were visually represented by means of errors plots and the proportions of different diagnoses in the case and control groups were depicted by a bar graph. As further analysis, Receiver Operating Characteristics (ROC) curves were constructed to estimate the usefulness of each haematological parameter in terms of sensitivity and specificity in predicting mortality. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Of 100 patients in study group, 60% were between 31-60 years of age and 8% were less than 30 years. The mean age among study group was 53.9 years (Standard deviation = 14.2). This was in comparison to the mean age among the control group which is 55 years (Standard deviation = 14.6). With regard to sex distribution, males constituted 77% and females were 23% in both the study and control groups. Cases with primary liver, heart and lung pathologies were more in the study (expired) group which was in contrast to the control group who had more of CNS and renal pathologies. The pattern of distribution and frequency of various diseases in each group is depicted in figure 1.

Figure 1. Distribution of cases and controls based on diagnosis

The values of various direct haematological parameters like haemoglobin, RBC count, RDW, TLC, MPV, platelet count and derived parameters like ANC, ALC, AMC, NLR, LMR and PLR were noted for both the study and control groups and their respective mean and standard deviation were shown in Table 1.

Blood Parameters	Status	N	Mean	SD	p value
Hb	Expired	100	10.8	3	0.08
	Control	100	11.6	2.7	
RBC	Expired	100	3.8	1.1	0.07
	Control	100	4	.9	
RDW	Expired	100	16.5	3.7	0.01
	Control	100	15.3	2.6	
TLC	Expired	100	16662	10068.1	<0.001
	Control	100	12324	4808.1	
ANC	Expired	100	13526.3	8424.1	<0.001
	Control	100	9546.7	4375.4	
ALC	Expired	100	1917	3902	0.5
	Control	100	1650	953.9	
AMC	Expired	100	966.9	887.4	0.2
	Control	100	840.2	509.8	
Platelet count	Expired	100	205.3	132.9	0.9
	Control	100	206.1	127.2	
MPV	Expired	100	7.9	1.2	0.2
	Control	100	7.7	1	
NLR	Expired	100	13.9	13.3	<0.001
	Control	100	8.4	7.7	
LMR	Expired	100	5	15	0.4
	Control	100	3.7	6.9	
PLR	Expired	100	215.9	224.6	0.09
	Control	100	168.3	168.2	

Table 1. Comparison of mean of haematological parameters in study and control groups

Baseline investigations revealed mean haemoglobin of 10.9 g/dl in the expired group compared to a higher mean haemoglobin of 11.5 g/dl in the control group. However, no statistically significant difference was noted. But when classifying according to the grade of anaemia we found that 21% of expired cases had severe anaemia in contrast to only 9% cases in the control group and was statistically significant ($p < 0.05$). The grading of anaemia in our study is shown in Table 2.

		Status				Chi square
		Control		Expired		P value
		Count	Column N %	Count	Column N %	
Anaemia grading	No anaemia	46	46.0%	37	37.0%	0.03
	Mild anaemia	9	9.0%	15	15.0%	
	Moderate anaemia	36	36.0%	27	27.0%	
	Severe anaemia	9	9.0%	21	21.0%	

Table 2. Grading of anaemia in study and control groups

The mean RBC count in the expired group was 3.8 millions/cu.mm (S.D. = 1.1) which was slightly lower than the mean of the control group, 4 millions/cu.mm (S.D. = 0.9). However, the difference was not statistically significant. With respect to RDW, a high mean RDW was seen in the expired group than the control group and were 16.5% (S.D. = 3.7) and 15.3% (S.D. = 2.6) respectively.

The overall mean TLC of the expired group was 16662/cu.mm and was found to be significantly higher than the control group whose mean was 12324/cu.mm. Analysis of ANC of both the expired and control groups revealed that expired group had a higher mean ANC of 13526.3/cu.mm when compared to a mean value of 9546.7/cu.mm in the control group. However, there were no statistically significant differences noted on comparing ALC and AMC between the two groups. In a similar manner no significant difference was noted in platelet count and MPV between the expired and control groups.

Of the three derived parameters, NLR showed a significant difference between the expired and control groups. The mean NLR of expired group was 13.9 which was higher than the mean NLR value of 8.4 in the control group. The p value was <0.001. Figure 2-5 display the error plots for the following parameters in order – RDW, TLC, ANC and NLR.

Figure 2. Error plot for red cell distribution width (RDW) in expired and control patients

Figure 3. Error plot for Total leucocyte count (TLC) in expired and control patients

Figure 4. Error plot for absolute neutrophil count (ANC) in expired and control patients

Figure 5. Error plot for Neutrophil lymphocyte ratio (NLR) in expired and control patients

ROC curves were plotted for parameters that were significant and relatively good curves for TLC, ANC and NLR were obtained. (Figure 6). The figure also showed that TLC, ANC, NLR and RDW were positively correlated with mortality whereas Hb and RBC count were negatively correlated. RDW $\geq 14.65\%$ (66% sensitivity and 50% specificity), total leucocyte count ≥ 12000 cells/cumm (66% sensitivity and 50% specificity), ANC ≥ 9156 cells/cumm (77% sensitivity and 50% specificity) and NLR ≥ 5 (sensitivity 80%, specificity 45%) predict mortality in critically ill patients.

Figure 6. ROC curve for RDW, TLC, ANC and NLR in predicting mortality of critically ill patients

DISCUSSION

Different methods are being followed by clinicians to categorize the patients' severity of illness and their disease outcome. But till date none of them is followed as a gold standard due to the complexity involved in scoring, non-availability and costliness of certain tests. However, mortality risk predictors are of interests to the clinicians, as it helps in identifying at-risk patients at an earlier stage and enable them to give special attention, intensive care and tailor-made therapy for better outcome of patients.

Of 100 expired cases, 60% were between 31-60 years of age. Prediction of mortality by age still remains controversial. Some studies suggested to include age as a parameter when assessing mortality,¹⁵ whereas study done by Chelluri et al proposed that age by itself does not appear to predict mortality in critically ill patients.¹⁶ Our study has found that RDW, TLC, ANC and NLR are independent predictors of mortality irrespective of the age, sex, diagnosis and other blood parameters.

In the current study, a higher mean RDW 16.5% was obtained which is in comparison with the study done by Felker et al which showed that RDW >15.8% had nearly a 2-fold increased risk of cardiovascular disease related death or as well as death from any cause. Similarly, Anderson et al reported that the risk of death over 1 year was 3 times higher in patients undergoing cardiac catheterization with RDW >14.0% whereas Tonnelli et al reported that death in coronary artery disease patients was twice as likely in patients with RDW >13.8% versus those with RDW <12.6%. Also, association of higher RDW with increased mortality risk has been reported by many studies involving patients with coronary artery disease, heart failure, septic shock, pulmonary embolism, cancer.^{12, 13} The exact physiologic mechanisms that relate RDW with survival are unknown. However, hypothesis stated that inflammatory factors elevated at terminal stages might alter erythrocyte homeostasis by inhibiting the production of or response to erythropoietin or by shortening red blood cell survival which increases RDW.^{12,17,18}

Higher TLC was found to be an independent predictor of mortality in the present study. Relevant studies in this field has also proved the same.^{19,20,21} The overall mean TLC of the expired group in the current study was 16662/cu.mm and was found to be significantly higher than the control group whose mean was 12324/cu.mm with a p value of <0.001. Study done by Asadollahi et al showed that more than 10,000/cumm of TLC had a positive relationship with mortality in general hospitalized patients which is in the lower range compared to our study.²² This difference could be due to selection of critically ill patients in our study compared to patients admitted in general wards in the earlier study. Analysis of ANC of both the expired and control groups revealed that expired group had a higher mean ANC of 13526.3/cu.mm when compared to the survived group. Similar results were reported in studies incorporating cardiovascular and haemodialysis patients.^{23,24} Out of all the haematological parameters included in the current study, NLR is the one which has been researched widely and detected as a valid tool in predicting postoperative patient outcome, overall survival, cancer disease-free survival and patient's sensitiveness to specific chemotherapy. A high mean

NLR (Mean: 14) was observed in the expired group compared to control group. Similar finding was observed in the study done by Saliccioli et al who had included 5,056 patients in their cohort study and the median NLR obtained for the entire cohort was 8.9 (interquartile range, 4.99 to 16.21). Thus, increasing quartiles of NLR increases the mortality risk. NLR has been shown to be associated with adverse events in stable coronary disease, long-term mortality in patients with ST-segment elevation myocardial infarction (STEMI), in-hospital and six-month mortality in acute coronary syndrome.^{6,7} This can explain the higher mortality rate of heart disease patients in ICU settings. Cut-off values calculated (RDW ≥14.65%, total leucocyte count ≥12000 cells/cumm, ANC ≥9156 cells/cumm and NLR ≥5) in the current study can be used as predictors of mortality in critically ill patients. However, sensitivity and specificity were slightly compromised due to the sample size. A study with high case load and inclusion of clinical and biochemical data might provide a much better and standard predictive tool of mortality.

CONCLUSION

Mortality risk prediction using simple CBC measurements is cost effective, easily available, less time consuming and simple to use. It also reduces clinician's variability in predicting mortality risk, improve diagnostic accuracy, triage patients, helps in giving appropriate treatment and family counseling regarding patient prognosis. Based on the findings observed herein, we suggest that higher RDW, TLC, ANC and NLR are independent predictors of mortality risk in critically ill patients and are to be tested in combination for a better prediction of mortality. Moreover, we have also observed that, detecting cases with RDW ≥14.65%, TLC ≥ 12000/cumm, ANC ≥ 9156/cumm and NLR ≥5 can individually predict mortality in critically ill patients. Using these cut-offs in combination might predict the mortality in a more precise manner. However more studies involving larger study group is necessary to validate these findings.

ACKNOWLEDGEMENT

We would like to express our gratitude to Dr. Rizwan who performed the statistical analysis for the study.

REFERENCES

- [1] Mihajlovic D, Lendak D, Mitic G, et al. Prognostic value of hemostasis-related parameters for prediction of organ dysfunction and mortality in sepsis. *Turkish Journal of Medical Sciences* 2015;45(1):93-8.
- [2] Bouch DC, Thompson JP. Severity scoring systems in critically ill. *Oxford J (Continuing Education in Anaesthesia Critical Care & Pain)* 2008;8(5):181-5.
- [3] Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Critical Reviews in Oncology Hematology* 2013;88(1):218-30.
- [4] Lee S, Oh SY, Kim SH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. *BMC Cancer* 2013;13:350.

- [5] Hung HY, Chen JS, Yeh CY, et al. Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. *International Journal of Colorectal Disease* 2011;26(8):1059-65.
- [6] Kaya H, Ertas F, Islamoglu Y, et al. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. *Clin Appl Thromb Hemost* 2014;20(1):50-4.
- [7] Núñez J, Nunez E, Bodi V, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol* 2008;101(6):747-52.
- [8] Riche F, Gayat E, Barthelemy R, et al. Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock. *Critical Care* 2015;19:439.
- [9] de Jager CP, Wever PC, Gemen EF, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One* 2012;7(10):e46561.
- [10] Shimada H, Takiguchi N, Kainuma O, et al. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. *Gastric Cancer* 2010;13(3):170-6.
- [11] Shao Y, Ning Z, Chen J, et al. Prognostic nomogram integrated systemic inflammation score for patients with esophageal squamous cell carcinoma undergoing radical esophagectomy. *Sci Rep* 2015;5:18811.
- [12] Tonelli M, Sacks F, Arnold M, et al. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation* 2008;117(2):163-8.
- [13] Patel KV, Ferrucci L, Ershler WB, et al. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med* 2009;169(5):515-23.
- [14] Kho AN, Hui S, Kesterson JG, et al. Which observations from the complete blood cell count predict mortality for hospitalized patients? *Journal of Hospital Medicine* 2007;2(1):5-12.
- [15] Ip SP, Leung YF, Ip CY, et al. Outcomes of critically ill elderly patients: is high-dependency care for geriatric patients worthwhile? *Crit Care Med* 1999;27(11):2351-7.
- [16] Chelluri L, Pinsky MR, Donahoe MP, et al. Long-term outcome of critically ill elderly patients requiring intensive care. *JAMA* 1993;269(24):3119-23.
- [17] Anderson JL, Ronnow BS, Horne BD, et al. Usefulness of a complete blood count-derived risk score to predict incident mortality in patients with suspected cardiovascular disease. *Am J Cardiol* 2007;99(2):169-74.
- [18] Felker GM, Allen LA, Pocock SJ, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol* 2007;50(1):40-7.
- [19] Cannon CP, McCabe CH, Wilcox RG, et al. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. *OPUS-TIMI 16 Investigators. Am J Cardiol* 2001;87(5):636-9, A10.
- [20] De Campos T, Cerqueira C, Kuryura L, et al. Morbimortality indicators in severe acute pancreatitis. *JOP* 2008;9(6):690-7.
- [21] Asadollahi K, Beeching NJ, Gill GV. Leukocytosis as a predictor for non-infective mortality and morbidity. *QJM* 2010;103(5):285-92.
- [22] Asadollahi K, Hastings IM, Beeching NJ, et al. Leukocytosis as an alarming sign for mortality in patients hospitalized in general wards. *Iran J Med Sci* 2011;36(1):45-9.
- [23] Furman MI, Becker RC, Yarzebski J, et al. Effect of elevated leukocyte count on in-hospital mortality following acute myocardial infarction. *Am J Cardiol* 1996;78(8):945-8.
- [24] Reddan DN, Klassen PS, Szczech LA, et al. White blood cells as a novel mortality predictor in haemodialysis patients. *Nephrol Dial Transplant* 2003;18(6):1167-3.