Original Article

Hematological Parameters Predicting Mortality in Patients with COPD Admitted to ICUs

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Abstract

Background: The prevalence of chronic obstructive pulmonary disease (COPD) is increasing in Saudi Arabia, yet there is a lack of studies on the usefulness of routine hematological parameters in predicting mortality.

Objective: To determine hematological parameters that can predict mortality in patients with COPD exacerbation admitted to intensive care units.

Materials and Methods: This multicenter retrospective study included patients with COPD admitted at intensive care units of Ministry of National Guard Health Affairs hospitals in Saudi Arabia between 2016 to 2021. Hematological parameters were used to predict mortality. ROC curve analysis was used to establish the threshold value of variables linked to risk of mortality and optimal cut-off points, and its sensitivity and specificity were determined.

Results: The study included 323 patients with COPD, of which 61% were females and the mean age was 72.7 (±12.7) years. The median length of hospital stay was 14 days (range: 6–26 days), and the overall mortality rate was 37.2%. After adjusting for gender and length of hospital stay in the multivariate analysis, independent predictors of mortality were age (OR: 1.029, 95% CI: 1.008–1.051; $P = 0.007$) and low mean corpuscular hemoglobin concentration (MCHC) (OR: 0.985, 95% CI: 0.970–1.000; $P = 0.047$). The ROC curve analysis revealed a cut-off value of 320.5 g/L for MCHC, with an AUC of 0.576.

Conclusion: This study found that in patients with COPD exacerbation admitted to ICU, older age likely increases the risk of mortality, whereas low MCHC likely decreases the risk of mortality. Further large-scale studies are required to validate these findings.

Keywords: Age, chronic obstructive pulmonary disease, exacerbation, hematological parameters, intensive care unit, mean corpuscular hemoglobin concentration, mortality

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent disorder that places significant burden on individuals and healthcare systems and was estimated to be the third highest cause of mortality globally in 2020.[1-7] In addition to continued treatment and management, including medication, pulmonary rehabilitation, and regular monitoring, patients with COPD are at an increased risk for comorbidities such as cardiovascular diseases, lung cancer, and mental health problems.[8-11] In addition, about 30% of patients with COPD require hospitalization, including to the intensive care unit (ICU), especially due to acute exacerbation of COPD, which is the sudden worsening of symptoms.[12-14] In Saudi Arabia, in 2019, the prevalence of COPD was 2053 cases per 100,000 population, a 49% increase compared with the prevalence reported in 1990.[15]

Precision medicine in COPD results in maximizing efficacy and minimizing side effects.[7] Biomarkers can play a role in precision medicine as well as in predicting mortality.[16] In COPD, the majority of blood-based biomarkers have been extensively studied in relation with exacerbations, disease progression, and mortality to aid in predicting mortality. [14,17,18] Neutrophil levels, C-reactive protein (CRP), tumor necrosis factor α, interleukin (IL) 6, IL-8, and fibrinogen are biomarkers that have been found to be useful in evaluating stability and exacerbation in patients with COPD.[19,20] Fibrinogen is considered a reliable biomarker for use in clinical trials because of its consistency and connection to variables related to COPD severity and prognosis, but is not considered to be useful in predicting the risk of COPD exacerbation.[21] Recent research suggests that alternative markers from regular blood tests, like the neutrophil lymphocyte ratio (NLR), platelet count, and platelet lymphocyte ratio (PLR) could be useful in evaluating the risk and severity of exacerbations in COPD. Additionally, these markers have shown as prognostic indicators for predicting hospital mortality associated with COPD exacerbation.[22,23] More recently, the number of eosinophils in peripheral blood has been reported to be useful in predicting the response to corticosteroids or the likelihood of exacerbation; however, studies have found contrasting results.[7,16,24] While additional biomarkers have been studied (such as anemia, hyponatremia, thrombocytosis, fibrinogen, and serum albumin level), literature regarding their systematic usage is weak.[7,25-28] The CRP/albumin ratio, which provides information on inflammation and nutritional status, appears to be a stronger predictor of prognosis in numerous disorders than each of these indicators individually.[7]

Despite the growing body of research, significant gaps remain in our understanding of how routine hematological parameters, particularly in diverse populations, can be used to predict mortality in COPD patients. There is a lack of such studies from Middle Eastern countries, where the epidemiology and clinical presentation of COPD may differ due to genetic, environmental, and healthcare-related factors. The present study aims to address these gaps by investigating the association between routine hematological parameters, including hemoglobin (Hgb), HgbA1C, mean corpuscular hemoglobin concentration (MCHC), and mortality in COPD patients admitted to ICUs across multiple hospitals in Saudi Arabia. By focusing on a Middle Eastern population, this study provides valuable insights into the prognostic value of these biomarkers in a region where COPD is increasingly prevalent, yet under-researched.

MATERIALS AND METHODS

Study design and participants

This retrospective study included all patients with COPD who were admitted to the ICU at Ministry of Health hospitals in three regions (Central, Western, and Eastern) of Saudi Arabia between 2016 and 2021. All data were retrieved from the BestCare electronic health records system.

This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center. This study was conducted in accordance with the Declaration of Helsinki, 2013, and local laws and regulations.

Inclusion and exclusion criteria

The inclusion criteria were patients with a confirmed diagnosis of COPD who were admitted to the ICU, irrespective of nationality or age. Patients with missing information were excluded from the study.

Laboratory data

The hematological parameters included in the current study were: Erythrocyte sedimentation rate, hematocrit, Hgb, HgbA1C, MCHC, mean corpuscular volume, mean platelet volume, red blood cell (RBC) count, red cell distribution width, partial thromboplastin time, prothrombin time, white blood cell (WBC) count, basophil count, eosinophil count, monocyte count, neutrophil count, lymphocyte count, NLR, platelet count, and PLR.

Statistical analysis

Statistical analysis was performed using SPSS software version 21 (IBM Corp. Chicago, IL, USA, version 21). The

normality of the data was assessed using the Shapiro–Wilk test. Unless stated otherwise, data were presented as the average ± standard deviation (SD) for normally distributed continuous variables and as median for skewed data. Data were summarized using median and interquartile ranges (IQR) for continuous data and percentages and frequencies for categorical data.

Univariate and multivariate logistic regression were used to determine laboratory values that could predict mortality in patients with COPD. Significant variables from the univariate analysis were incorporated into the multivariate regression analysis. ROC curve analysis was used to establish the threshold value of variables linked to mortality risk. Statistical significance was reported using a *P* value of ≤ 0.05 and an odds ratio (OR) with a 95% confidence interval (CI).

RESULTS

A total of 323 patients with COPD patients were included, of which 61% were females and the mean (±SD) age was 72.7 (±12.7) years. The median (IQR) length of stay was 14 (range: 6–26) days. Descriptive statistics for RBC, WBC, and coagulation parameters are detailed in Table 1. The mortality rate in the study population was 37.2%. The mean age of patients who died was higher than those who survived (75 ± 11 years vs. 71.3 ± 13.5 years, respectively).

In the univariate analysis, the only significant factors associated with mortality were increased age ($P = 0.013$) and low MCHC ($P = 0.05$). Patients who died had lower MCHC value than those who survived (318 g/L [range: 307–329 g/L] vs. 322.5 g/L [range: 313–333 g/L], respectively). In the multivariate analysis, after adjusting for gender and length of hospital stay, the predictors of mortality were age (OR: 1.029, 95% CI: 1.008–1.051, $P = 0.007$) and low MCHC (OR: 0.985, 95% CI: 0.970–1.000, $P = 0.047$) [Table 2].

In the ROC curve analysis for MCHC (g/L) value in predicting the mortality among the COPD patients, the area under the curve was 0.576 and the cut-off value was 320.5 g/L [Figure 1]. The sensitivity and specificity for MCHC values were 55% and 45%, respectively. Further, the positive predictive value was 44% and the negative predictive value was 68%.

DISCUSSION

This study found that age and low MCHC were independent predictors of mortality in patients with COPD who were admitted to the ICU. While older age was found to increase the risk of mortality, surprisingly, low MCHC values were found to decrease the risk of mortality. The current study design does not allow determining the reason of lower MCHC resulting in reducing the risk of mortality in COPD patients, and this warrants further research. The age-related findings align with earlier studies that found age to be a significant risk factor for death in this population.[24]

Anemia significantly impacts the clinical course of a variety of chronic disorders, and chronic diseases are believed to be responsible for anemia due to chronic inflammation and inadequate hematological function, specifically iron deficiency.[29] A reduction in MCHC indicates a reduction in hemoglobin per RBC, and thus decrease in oxygen-carrying ability.[30,31] Patients with chronic systolic and symptomatic

Table 1: Descriptive statistics for demographic and hematological parameters (*N*=323)

Particulars	Descriptive statistics[a]
Age (years)	72.67±12.69
Gender	
Male	126 (39)
Female	197 (61)
Length of stay (days)	14 (6–26)
RBC parameters	
ESR	59.07±33.68
Hematocrit	0 (0–0.35)
Hgb	108.75±24.16
HgbA1C	7.7 (6–9.25)
MCHC	321 (310–331)
MCV	89.1 (85–93.9)
MPV	8.05 (7.6–9.58)
RBC count	3.86±0.87
RDW	15.78±2.90
PTT	34.34±13.48
PT	14.96±9.68
WBC parameters	
WBC count	10 (7–15)
Basophil count	0 (0–0)
EOS count	0 (0–0.01)
Mono count	0.60±0.62
Neutrophil count	9.10±6.53
Lymph count	1 (0.6–1.42)
NLR	7 (4.29–11.04)
Coagulation parameter	
Platelet count	217 (154.25–292.50)
PLR	232 (134.35–309.31)
Mortality	
Alive	203 (62.8)
Died	120 (37.2)

[a]For continuous variable, mean±SD for normally distributed data and median (IQR) for skewed data; for categorical variable, frequency and percentage. ESR – Erythrocyte sedimentation rate; Hgb – Hemoglobin; HgbA1C – Hemoglobin A1C; MCHC – Mean corpuscular Hgb concentration; MCV – Mean corpuscular volume; MPV – Mean platelet volume; RBC – Red blood cells; RDW – Red cell distribution width; PTT – Partial thromboplastin time; PT – Prothrombin time; WBC – White blood cells; SD – Standard deviation; IQR – Interquartile range; NLR – Neutrophil lymphocyte ratio; PLR – Platelet lymphocyte ratio

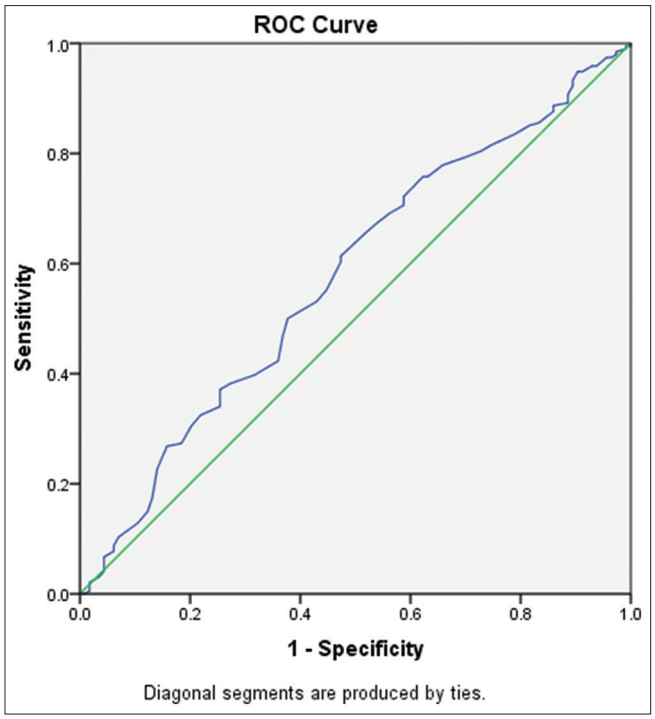

Figure 1: Receiver operating characteristic (ROC) curve analysis for mean corpuscular hemoglobin concentration in predicting mortality for chronic obstructive pulmonary disease

heart failure with a decreased MCHC in their peripheral blood have a worse prognosis, which includes death, transplantation, and hospitalization due to heart failure. This association remains significant regardless of age, cardiac function, renal function, and severity of heart failure. Low levels of hemoglobin are frequently found in patients with COPD.[32] Further, a recent study has found that low MCHC value is an independent predictor of increased risk of mortality in patients with COPD exacerbation,[33] which is in contrast to the findings of the current study.

Platelet levels rise with inflammation, and thus are useful as biomarkers. A study found that patients who died had higher platelet-to-lymphocyte ratio than those who survived (382.2 + 392.6 vs. 270.5 + 155.5, respectively).[22] The current study also found that the platelet-to-lymphocyte ratio was non significantly higher in patients who died (235.7 [IQR]: 127–323.3 vs. 228.84 [IQR: 124.5–307.5], respectively.

A study found that in patients with chronic heart failure, the association between MCHC and prognosis was significantly stronger in non-anemic patients than anemic patients, signifying that relative hypochromia should be considered even if anemia is not present. This study also found that patients with persistently low MCHC (<33.6 g/dL) had significantly higher risk of mortality compared with patients in three groups of MCHC value ≥33.6 g/dL.[34,35] Based on these findings, we believe that the patients in our study had a lower mean MCHC value of 31.6 g/dL than those in earlier studies.[33,35] Few studies have also reported that MCHC is related to a patient's prognosis after their COPD exacerbation, yet few patients receive treatment for iron deficiency.[36]

COPD, an inflammatory lung disease, and systemic inflammation both lower functional iron levels. Although anemia is the result of iron deficiency, individuals without a diagnosis of anemia may yet have non-anemic iron insufficiency. Iron deficiency can occur before a COPD flare-up if the MCHC levels are low. However, the exact reasons for the association between MCHC and the chronic conditions such as COPD or heart disease remain unclear. Prior studies have shown that MCHC indicates low iron levels and persistent inflammation contributes to iron deficiency.[37] Therefore, the level of MCHC reduction may correlate with the level of inflammation. Moreover, patients with COPD and iron deficiency have been reported to experience reduced exercise capacity, and insufficient physical activity has been associated with a poor outcome.[37]

Limitations

A limitation of this study was that data regarding patients' intake of iron, vitamin B12, and folic acid, as well as their daily diet and nutritional administration upon admission because of the worsening condition was not available, and thus could not be assessed as potential factors for anemia, iron deficiency, and decreased MCHC levels. Further epidemiological and prospective studies are needed to examine how dietary intake impacts anemia, iron deficiency, and MCHC levels, which can be measured along with peripheral blood cell counts.[29]

Another limitation of the study is that the causes or indications for ICU hospitalization were not available. Further, the study did not group patients according to survival status. There is also need for additional research to fully understand the U-shaped association between Hb levels and mortality. Although this study found that age is an independent predictor of mortality, potential differences in risk across different age groups were not studied. The lack of stratified data confines our capacity to draw more nuanced findings about how age influences mortality risk in different demographic groups. Large-scale studies are required to validate the findings of this study. In addition, future studies could assess the usefulness of combining various biomarkers to assess the severity of pulmonary illnesses.[38]

Table 2: Logistic regression analysis for the various parameters with mortality in chronic obstructive pulmonary disease patients

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographic variables				
Age (years)	1.026 (1.005–1.046)	0.013*	1.029 (1.008–1.051)	0.007*
Length of stay (days)	1.002 (0.994–1.010)	0.614		
Gender	0.720 (0.451–1.152)	0.171		
RBC parameters				
ESR	1.003 (0.991–1.014)	0.633		
Hematocrit	1.153 (0.344–3.3865)	0.817		
Hgb	0.994 (0.984–1.004)	0.218		
HgbA1C	0.819 (0.564–1.190)	0.295		
MCHC	0.985 (0.970–1.000)	0.050*	0.985 (0.969–1.000)	0.047*
MCV	1.008 (0.980–1.036)	0.584		
MPV	0.930 (0.807–1.072)	0.316		
RBC count	0.969 (0.742–1.266)	0.818		
RDW	0.989 (0.913–1.072)	0.792		
PTT	1.013 (0.995–1.031)	0.164		
PT	1.003 (0.979–1.028)	0.798		
WBC parameters				
WBC count	0.980 (0.950–1.011)	0.209		
Basophil count	0.514 (0.031–8.465)	0.642		
EOS count	0.778 (0.088–6.876)	0.821		
Mono count	1.092 (0.700–1.704)	0.698		
Neutrophil count	0.994 (0.951–1.039)	0.788		
Lymph count	1.146 (0.821–1.598)	0.424		
NLR	0.988 (0.964–1.013)	0.345		
Coagulation Parameters				
Platelet count	1.000 (0.998–1.001)	0.615		
PLR	1.000 (0.999–1.001)	0.971		

*Statistically significant at 5%. OR – Odds ratio; 95% CI – 95% confidence interval; RBC – Red blood cells; ESR – Erythrocyte sedimentation rate; Hgb – Hemoglobin; HgbA1C – Hemoglobin A1C; MCHC – Mean corpuscular Hgb concentration; MCV – Mean corpuscular volume; MPV – Mean platelet volume; RBC – Red blood cells; RDW – Red cell distribution width; PTT – Partial thromboplastin time; PT – Prothrombin time; WBC – White blood cells; NLR – Neutrophil lymphocyte ratio; PLR – Platelet lymphocyte ratio

CONCLUSION

This study found that age and low MCHC were independent predictors of mortality in patients with COPD exacerbation who were admitted in the ICU. Older age was found to increase the risk of mortality, whereas low MCHC was found to decrease the risk of mortality. Future studies should validate these results and explore the integration of MCHC and other hematological markers into comprehensive prognostic models for COPD.

Ethical considerations

This study was approved by the Institutional Review Board of the King Abdullah International Medical Research Center (Protocol no.: NRC22R-304-06; date: June 27, 2022). Requirement for patient consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: B.A.A., M.H.A., A.M.A; Methodology: A.M.A., M.S.A, M.A.A, F.J.A., A.Z.A.; Data analysis: W.P., M.H.A., A.M.A, B.A.A.; Writing – review and editing: B.A.A., M.H.A., A.M.A, A.S.A., R.S.A., A.M.A, W.P, T.S.A., N.M.A., T.T.I., T.F.A., N.A.S.; Supervision: B.A.A., M.H.A., A.M.A.

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Conflicts of interest

There are no conflicts of interest.

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