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The Relationship Between Mortality and Hemoglobin Levels in Intensive Care Patients with Acute Respiratory Distress Syndrome

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ABSTRACT

Objective: Low hemoglobin levels are associated with an increased risk of mortality in intensive care unit (ICU) patients. The underlying reason is due to the limitation in oxygen delivery to the tissues caused by a reduction in the number of oxygen carrying erythrocytes. This study aimed to examine the relationship between decline in hemoglobin level (DHgb=Admission hemoglobin – nadir hemoglobin), nadir hemoglobin levels (NdrHgb; the lowest hemoglobin value during ICU stay) and mortality in COVID ARDS patients admitted to ICU.

Methods: This was a prospective nonrandomized study of consecutive COVID ARDS patients who had at least two determinations of hemoglobin level (the first on admission) separated by 24 hours and an ICU stay <14 days. Admission hemoglobin (AdmHgb), NdrHgb and DHgb levels were analyzed. Data on blood transfusions were also collected.

Results: Although high DHgb and low NdrHgb levels were significantly associated with mortality in univariate analysis of patients, this was not sustained in multivariate analysis. The area under the ROC curve (AUC) of DHgb was 0.577, with a cut-off value of 1.9 g/dl, sensitivity and specificity were 50.7%, and 65.2%, respectively. NdrHgb had a cut-of value of 10.7 g/dl, with an AUC of 0.423, sensitivity and specificity of 50%.

Conclusion: Our results showed that DHgb and low NdrHgb levels are both predictive markers for mortality with moderate sensitivity and specifity. We recommend further studies evaluating a simple scoring model based on DHgb and NdrHgb for predicting mortality

Keywords: ARDS, nadir hemoglobin, drop, deltahemoglobin, mortality

Introduction

Anemia is a common clinical problem in critically ill patients and it can lead to multiple adverse outcomes. Nearly 95% of patients are anemic by day three after intensive care unit (ICU) admission (1–3). Diagnosis of anemia is based on hemoglobin levels although it is not the hemoglobin level per se that determines the severity of the anemia but the imbalance between oxygen delivery and consumption (4).

The balance between oxygen delivery and consumption is very essential and can be impaired by myriad factors, like decrease in hemoglobin levels. Impairment of this balance is associated with increased mortality (5). In this study we aimed to investigate whether admission hemoglobin, nadir hemoglobin levels and decline in hemoglobin level predict ICU mortality in critically ill COVID-ARDS patients.

Materials and methods

Study design

This prospective nonrandomized, single-center study was carried out on all COVID-19 ARDS patients in our 48-bed adult ICU, between September 2021 and September 2022. The study was approved by the Ethics Commitee of Ankara City Hospital. All consecutive patients who had at least two determinations of hemoglobin level (the first on admission) separated by 24 hours were included while those who had a prolonged stay (>14 days) in the ICU were excluded to avoid the bias of an expanded length of ICU stay. Patients who were need for a surgical intervention was exclueded. In patients who were readmitted to the ICU only the first admission was considered.

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Hemoglobin measurements

Hemoglobin levels were measured on admission and every 24 h thereafter while the patient stayed in the ICU. Admission hemoglobin (AdmHgb), nadir hemoglobin (NdrHgb; the lowest hemoglobin value during ICU stay) and decline in hemoglobin level (DHgb=Admission hemoglobin – nadir hemoglobin) were analyzed. Data on blood transfusions were also recorded.

Data collection and endpoint

Clinical, analytical and demographic data were prospectively extracted using dedicated software used in our hospital. Admission lactate levels were also recorded. There was not a cut off value for transfusion decision.

Blood Transfusion Practice

At our ICU, decisions about transfusion are at the discretion of the attending physician. There are no specific levels that trigger a blood transfusion.

Statistical analysis

Analysis was carried out using IBM Statistical Package for Social Sciences (SPSS) program version Statistics Version 24. The chi-square test, Fisher's exact test, Student's t-test, Mann–Whitney U-test and multivariate logistic regression analysis were used where appropriate. In the descriptive analysis, values are presented as mean ± standard deviation (median; min-max). For comparison of dichotomous variables between groups, the chi-square test or Fisher's exact test was used. Comparisons of continuous variables between two groups were made with the Mann–Whitney U test. Multivariable logistic regression using backward selection was used to determine the independent predictors for in-hospital mortality with a cutoff of p >0.05 for removal. Two models were fit; chronic heart failure, neurologic diseases, age, APACHE II score, requirement of mechanical ventilation, hemodiafiltration (HDF) or transfusion, NdrHgb and admission lactate levels were included in the first model. NdrHgb were replaced by DHgb in the second model. The Hosmer-Lemeshow Test was used as goodness of fit index. To avoid possible multicollinearity, only one of the highly correlated variables was included in each model.

Finally, the receiver operating characteristic (ROC) curve was applied to determine the ideal cut-off values of hemoglobin and admission lactate for mortality. The test characteristics of the different cut-off values, including sensitivity, specificity, area under the curve (AUC) were also examined. Statistical significance was defined at the p <0.05 level.

Results

During the study period, 1035 adult COVID-19 ARDS patients were hospitalized in our 24-bed ICU. Of these, 712 had two determinations of hemoglobin level (the first on admission) separated by 24 hours and an ICU stay of ≤14 days.

Table 1. Characteristics of survivors and non-survivors

	Survivors (n=355)	Non-survivors (n=357)	Total (n=712)	*p*
Gender (F)	146(41.1%)	147 (41.2%)	293(41.2%)	0.989
Comorbidities				
HT	190 (53.5%)	204 (57.1%)	394 (55.3%)	0.331
DM	131 (36.9%)	132 (37.0%)	263 (36.9%)	0.984
CAD	91 (25.6%)	114 (31.9%)	205 (28.8%)	0.063
CHF	15(4.2%)	35 (9.8%)	50 (7.0%)	0.004
Arrhytmia	16 (4.5%)	24 (6.7%)	40 (5.6%)	0.199
Respiratory diseases	61 (17.1%)	61 (17.1%)	122 (17.1%)	0.973
Renal diseases	36 (10.1%)	37 (10.4%)	73 (10.3%)	0.922
Neurologic diseases	41 (11.6%)	65 (18.2%)	106 (14.9%)	0.013
Malignancy	22 (0.06%)	32 (9.0%)	54 (7.6%)	0.163
Rheumatological diseases	6 (1.7%)	7 (1.7%)	13 (1.8%)	0.787
Thyroid diseases	21 (5.9%)	16 (4.9%)	37 (5.2%)	0.389
Others	32 (9.0%)	27 (7.6%)	59 (8.3%)	0.483
None	61(17.2%)	54 (15.1%)	115 (16%)	0.456
Age (years)	64.6±14.2 (65.0; 23–93)	72.7±12.5 (73.0; 25–97)	68.7±14.0 (71.0; 23–97)	0.000
APACHE II	9.3±3.1(9.0; 4–16)	28.7±6.9 (30.0; 2–41)	19.0±11.1 (15.0; 2–41)	0.000
Length of stay (days)	7.5±3.5 (7.0; 2–14)	7.2±3.8 (7.0; 2–14)	7.3±3.6(7.0; 2–14)	0.185
Anemia at admission	148 (41.7%)	164 (45.9%)	312 (43.8 %)	0.253
Anemia during ICU stay	269 (75.8%)	290 (81.2%)	559 (78.5 %)	0.077
Requirement of mechanical ventilation	9 (2.5%)	348 (97.5%)	357 (50.1%)	0.000
Requirement of HDF	21 (5.9%)	118 (33.4%)	139 (19.7%)	0.000
Transfusion	19 (5.4%)	39 (10.9%)	58 (8.1%)	0.007

* F: Female; HT: Hypertension; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; CHF: Chronic Heart Failure; HDF: Hemodiafiltration; **APACHE:** acute physiology and chronic health evaluation score

** Values are expressed as "mean+sd (median; min-max)" or as percentages.*

Table 2. Labaratory parameters of survivors and non-survivors

	Survivors (n=355)	Non-survivors (n=357)	Total	
Characteristics	Mean+SD (Median; Min-Max)	Mean+SD (Median; Min-Max)	Mean+SD (Median; Min-Max)	*p*
AdmHgb (g/dl)	12.7±2.1 (12.8; 4, 9–20, 6)	12.6±2.3 (12.7; 5, 8–18, 6)	12.6±2.2 (12.8; 4, 9–20, 6)	0.471
AdmLact (mmol/L)	2.0±1.2 (1.8; 0, 2–14, 2)	2.4±1.4(2.0; 0, 5–14, 6)	2.2±1.3 (1.9; 0, 2–14, 6)	0.000
NdrHgb (g/dl)	11.1±2.1 (11.3; 4, 9–17, 5)	10.5±2.3 (10.7; 5, 4–17, 0)	10.8±2.2 (11.0; 4, 9–17, 5)	0.000
DHgb (g/dl)	1.6±1.3 (1.4; -0, 8–7, 2)	2.0±1.7 (1.9; -0, 6–8, 6)	1.8±1.5 (1.6; -0, 8–8, 6)	0.000

*__AdmHgb:__ Admission hemoglobin; __AdmLact:__ Admission lactate; __NdrHgb:__ Nadir hemoglobin; __DHgb:__ Decline in hemoglobin level

Table 3. Multiple stepwise logistic regression analysis for predicting mortality of patients

COVARIANTS	P	Exp (B)	CI 95% Lower-Upper
Age	0.000	0.897	0.845–0.953
APACHE II	0.000	1.649	1.387–1.961
Requirement of Mechanical Ventilation	0.000	0.004	0.000–0.026
Requirement of HDF	0.259	2.708	4.79–15.297
Constant	0.65	329.756	

*__HDF:__ Hemodiafiltration
*__Included variables:__ chronic heart failure, neurologic diseases, age, APACHE II score, requirement of mechanical ventilation, hemodiafiltration or transfusion, decline in hemoglobin level

Table 4. The cut-off, sensitivities, specificities, Youden's index and area under curve of each variable for predicting mortality

Variables	Cut-off	Sensitivity (%)	Specifity (%)	Youden's index	AUC (95%CI)	p
AdmHgb (g/dl)	12.7	50.4	49.6	0	0.483 (0.440–0.526)	0.435
NdrHgb (g/dl)	10.7	50.0	50.0	0	0.423 (0.381–0.466)	0.000
DHgb (g/dl)	1.9	50.7	65.2	0.09	0.577 (0.535–0.620)	0.002
AdmLact (mmol/L)	1.9	50.3	57.9	0.08	0.573 (0.531–0.616)	0.001

*__AUC:__ Area under the ROC curve; __AdmHgb:__ Admission hemoglobin; __MaxHgb:__ Maximum hemoglobin; __NdrHgb:__ Nadir hemoglobin; __DHgb:__ Decline in hemoglobin level; __AdmLact:__ Admission lactate

The demographic and clinical characteristics of survivors and non-survivors are compared in Table 1. There were 355 (49.9%) survivors and 357 (50.1%) non-survivors.

AdmHgb, NdrHgb, DHgb and admission lactate levels were compared between survivors and non-survivors. Non-survivors had significantly higher admission lactate, DHgb and lower NdrHgb levels (Table 2).

First model of backward logistic regression analysis did not fit well (Hosmer-Lemeshow Test; p=0.000). Second model revealed that; age, APACHE II score and requirement of mechanical ventilation and HDF significantly predict mortality (Hosmer-Lemeshow Test; p=0.089). CHF, neurologic diseases, transfusion, AdmLact and Dhgb were excluded from the model by the backward procedure.

Figure 1 illustrates ROC curves for AdmLact, AdmHgb, NdrHgb and Dhgb to predict mortality. DHgb has the highest average area under curve (AUC) value (0.577) followed by AdmLact (0.573). (Table 4).

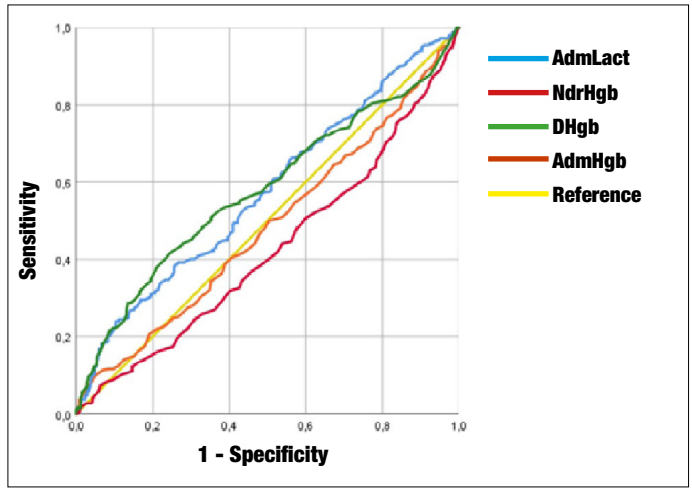

Figure 1. Receiving operating characteristic (ROC) curves for assessing the predictive accuracy of AdmHgb, MaxHgb, NdrHgb, DHgb and admission lactate for mortality

Discussion

In this prospective nonrandomized study of 712 patients admitted to the ICU for COVID-19 ARDS, we demonstrated that DHgb and NdrHgb levels are associated with mortality. We also found that these two parameters have moderate sensitivity and specifity for predicting mortality, even if predictive sensitivity and specifity of DHgb level were better than admission lactate levels in this cohort of patients.

According to the World Health Organization, anemia is defined as a low hemoglobin concentration (<13 g/dL in men, <12 g/dL in women) (6). Resulting from multiple causes; it is a frequent occurrence in critically ill patients such that up to 77% of patients experience anemia during their ICU stay (7). Although the diagnosis of anemia relies on hemoglobin level; its association with adverse outcomes and considerable morbidity can be explained on the basis of tissue oxygenation. Anemia can reduce oxygen delivery, causing tissue ischemia, anerobic metabolism, cellular acidosis and multiple organ dysfunction (8–10).

Intensive care patients can develop anemia due to multiple mechanisms including pathophysiological and iatrogenic factors. Pathophysiological factors include; inflammation which impairs erythropoiesis, reduces erythrocyte maturation and life span; dysfunction of kidney with low erythropoietin levels; dysregulation of iron metabolism; nutritional defficiencies (iron, vitamin B12, folate); fluid shift; major and minor hemorrhages; coagulopathies (thrombocytopenia, liver dysfunction). As expected; frequent and large volume of phlebotomies; hemolysis due to extracorporeal therapies; coagulopathies (pharmacotherapy); insufficient enteral feeding; invasive interventional procedures; fluid therapies are main examples of iatrogenic factors that causes anemia in ICU patients (11). As a result; the estimated blood loss is much higher in this group of patients than in patients who are hospitalised in other wards (12,13).

Following an acute impairment of oxygen delivery to the tissues, compensatory mechanisms such as an increase in heart rate or an increase in oxygen extraction are activated in order to meet oxygen requirements (14). A reduction in hemoglobin levels can cause a reduction in oxygen delivery, depending on the capacity of these compensatory mechanisms. In critical illness, most of the compensatory mechanisms for anemia can be reduced. Therefore the magnitude of decline in hemoglobin levels gains more importance in critically ill patients (15).

Although high DHgb and low NdrHgb levels were significantly associated with mortality in univariate analysis of our cohort, this was not sustained in multivariate analysis. Further investigation in a larger cohort of this group of patients may reveal the predictive importance of DHgb and NdrHgb. Another explanation is possible necessity for a simple scoring model that includes both DHgb and NdrHgb for prediction of morbidity and mortality. A high DHgb level may be less important in case of a high NdrHgb level, even if the same DHgb level would be a strong predictor for morbidity and mortality with a lower NdrHgb level. Additionally, our ROC curve analysis showed DHgb has largest AUC, highest specificity and sensitivity of predicting mortality, in comparison to admission lactate and NdrHgb.

Prognostic implications of DHgb and NdrHgb have been studied in different patient groups. A study with 7781 acute coronary syndrome patients who were managed invasively concluded that an in-hospital drop of hemoglobin ≥3 g/dl, even in the absence of overt bleeding, is common and is independently associated with increased risk for one year mortality (16). Diedler et al. studied the impact of admission, nadir and mean (calculated from all available values) hemoglobin levels on functional outcome and mortality in 196 non-traumatic intracerebral hemorrhage patients and reported an independent association between low mean hemoglobin levels and worse functional outcomes, although hemoglobin levels during hospital stay were not predictive of in-hospital mortality (17). We did not analyze the association between the worse outcomes and hemoglobin levels which can be considered as a limitation of the study.

Although our study did not focus on the diagnosis of anemia, but on NdrHgb level instead; the prevalence of anemia in our study patients was 43.8% at admission and increased to 78.5% during ICU stay, which means 247 of 400 nonanemic patients develop hospital acquired anemia (HAA) in our cohort. In a study with 2909 nonanemic acute myocardial infarction (AMI) patients; 45.4% of the patients developed HAA, the majority (86.5%) of which did not have any documented in-hospital bleeding. The development of moderate and severe HAA was associated with higher mortality and worse health status in the first year after AMI, independent of documented in-hospital bleeding (18).

In conclusion, in our study, DHgb and NdrHgb levels were associated with mortality in COVID-ARDS patients admitted to ICU. Although sensitivity and specificity for predicting mortality were moderate for both of them, a simple scoring model based on DHgb and NdrHgb may have higher predictive value for in-hospital mortality in this group of patients. Further studies are warranted with larger sample sizes.

AUTHOR CONTRIBUTIONS:

Concept: BT, BDK, MC, AED, AY, NMM; **Design:** BT, BDK, MC, AED, AY, NMM; **Supervision:** BT, NMM; **Funding:** BT; **Data Collection and/or Processing:** BDK, BT, MC; **Analysis and/or Interpretation**: BT, AED; **Literature Search:** BT; **Writing Manuscript**: BT; **Critical Review:** NMM.

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