

Lower mean corpuscular hemoglobin concentration is associated with poorer outcomes in intensive care unit admitted patients with acute myocardial infarction

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Background: Accumulated studies have shown that hematological parameters [e.g., red blood cell distribution width (RDW), hemoglobin, platelet count] and serum potassium level can impact the prognosis of patients with acute myocardial infarction (AMI). However, no previous study has evaluated the prognostic values of these laboratory tests simultaneously.

Methods: This study is based on an intensive care unit (ICU) database named Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II). Adult patients with AMI were included, and their hematological parameters and serum ion levels on admission were extracted. The relationships between these laboratory tests and hospital mortality were evaluated using a logistic regression model and receiver operating characteristic (ROC) curve analysis. The effects of these laboratory tests on 1-year mortality were evaluated using a Cox hazard regression model and Kaplan-Meier curve analysis.

Results: In univariable analysis, increased white blood cell (WBC), neutrophil percentage, mean corpuscular volume (MCV), RDW, potassium and decreased red blood cell (RBC), hemoglobin, mean corpuscular hemoglobin concentration (MCHC), hematocrit and percentage of lymphocyte, monocyte, basophil and eosinophil were significantly associated with hospital mortality. In multivariable analyses, basophil percentage, potassium, WBC and MCHC were independently associated with hospital mortality, while WBC, RDW, MCHC, potassium and percentages of neutrophil and lymphocyte were associated with 1-year mortality.

Conclusions: Hematological parameters and serum potassium can provide prognostic information in AMI patients. MCHC is an independent prognostic factor for both short and long term outcomes of AMI.

Keywords: Acute myocardial infarction (AMI); mean corpuscular hemoglobin concentration (MCHC); hematological parameter; potassium; prognosis

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Introduction

Hematological parameters, easily obtained with low cost using the modern hematological analyzers, are widely used in risk stratification, diagnosis, and prognosis estimation for patients with cardiovascular diseases (1-3). For example,

higher red blood cell distribution width (RDW) (4), neutrophil to lymphocyte ratio (5), mean corpuscular volume (MCV) (6), platelet count (7) and white blood cell (WBC) (8) count are associated with poorer outcomes in patients with acute myocardial infarction (AMI), while decreased

hemoglobin is associated with higher mortality (9). In addition, serum potassium level can also impact the outcomes of AMI patients (10,11). Since these routine laboratory tests are usually mutually correlated (e.g., WBC and RDW (12), RDW and hemoglobin (12), platelet count and potassium (13), platelet count and RDW (14), neutrophil count and RDW (15), the confounding effects of another tests cannot thus be ignored when the prognostic value of an interesting test is evaluated. However, no previous study has evaluated the prognostic values of these laboratory tests simultaneously to the best of our knowledge.

In this study, we studied the prognostic values of hematological parameters and serum ion levels (including potassium, sodium and chloride) in adult AMI patients admitted to intensive care unit (ICU).

Materials and methods

Data source

Similar to our previous work (16), this study is based on a publicly accessible critical care database named Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) (17). This database consisted of more than 30,000 patients admitted to ICU of Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) from 2001 to 2008 (18). Clinical variables, including demographics characteristics, laboratory tests, microbiological findings and outcomes were all recorded in this database. Accessing process for MIMIC II was well documented by Dr. Zhang (19).

The establishment of this database is approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA) and BIDMC. All patients in this database are de-identified to protect their privacy. Therefore, patients consent was waived in this study.

Data extraction

Structure query language (SQL) with pgAdmin (version 1.12.3), an open source development and administration platform for PostgreSQL, was used to extract data from MIMIC II. We restricted the search to adult patients (more than 15 years old) with AMI using International Classification of Diseases (ICD)-9 code between 410.00 and 410.92. The order or priority of ICD-9 code was not limited.

Hematological parameters on admission were extracted, including WBC and its subpopulations, red blood cell (RBC) and its indices [MCV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, hematocrit and hemoglobin] and platelet count. In addition, serum sodium, potassium, chloride levels and simplified acute physiology score I (SAPS I) were also extracted.

For patients admitted to ICU for more than one time, only data of initial admission were used. If patients received a laboratory test more than one time during their hospitalization, only the initial test results were included.

Statistical analyses

Mann-Whitney U test was used to compare continuous variables because all of them were not normally distributed. Chi-square test was used to compare categorical variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of laboratory tests for hospital mortality. Forward conditional logistic regression model was used to analyze the association between laboratory tests and hospital mortality. The long term prognostic values of laboratory tests were evaluated using Cox hazard regression model and Kaplan-Meier curve analysis. All analyses were performed using SPSS 18.0, and a P value less than 0.05 was considered statistically significant.

Results

Characteristics of subjects

As shown in *Table 1*, 3,304 subjects were included in this study. A total of 427 subjects died in hospital (hospital non-survivors) and their clinical characteristics were compared with hospital survivors. Generally, hospital non-survivors were older and had significantly higher WBC count, neutrophil percentage, MCV, RDW, potassium and SAPS I ($P < 0.01$ for all), while their RBC, hemoglobin, MCHC, hematocrit, percentages of lymphocyte, monocyte, basophil and eosinophil were significantly lower ($P < 0.01$ for all). Therefore, these laboratory tests were included into further analyses.

Predictive value of hematological parameters and potassium for hospital mortality

Table 2 lists the areas under ROC curves (AUC) of

Table 1 Characteristics of the subjects

Characteristics	Hospital survivors (n=2,877)		Hospital non-survivors (n=427)		P value
	n	Results	n	Results	
Age (years)	2,877	71±23	421	77±12	<0.001
Gender (M/F)	2,874	1,785/1,089	421	226/195	0.001
WBC (10 ⁹ /L)	2,864	11.7±5.4	416	13.2±10.2	<0.001
Neutrophil (%)	1,918	77.4±12.2	350	77.5±17.4	0.001
Lymphocyte (%)	1,918	15.0±10.2	350	12.8±12.4	<0.001
Basophil (%)	1,918	0.33±0.34	350	0.23±0.32	<0.001
Monocyte (%)	1,918	4.5±2.4	350	4.4±4.0	0.005
Eosinophil (%)	1,918	1.29±1.72	350	0.97±1.97	<0.001
RBC (10 ¹² /L)	2,682	4.04±0.70	416	3.89±0.67	<0.001
Hemoglobin (g/L)	2,864	122.4±21.5	416	117.5±19.4	<0.001
MCV (fL)	2,862	89±6	416	91±7	<0.001
MCH (pg)	2,862	30.4±2.3	416	30.3±2.4	0.457
MCHC (g/L)	2,863	341.7±14.4	416	334.1±14.8	<0.001
RDW (%)	2,862	14.09±1.64	416	14.76±1.84	<0.001
Hematocrit (%)	2,865	35.83±5.87	417	35.16±5.59	0.004
Platelet (10 ⁹ /L)	2,864	248±104	417	245±112	0.360
Sodium (mmol/L)	2,855	138.4±4.1	412	138.6±5.4	0.260
Potassium (mmol/L)	2,859	4.2±0.7	412	4.5±0.9	<0.001
Chloride (mmol/L)	2,855	103.0±5.2	413	103.1±6.7	0.310
SAPS I	2,693	13.1±5.6	366	18.6±5.6	<0.001

WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; SAPS I, simplified acute physiology score I.

hematological parameters and potassium. SAPS I, a well-known prognostic factor for critical ill patients, had the highest AUC, followed by MCHC, RDW, basophil, WBC, lymphocyte percentage, eosinophil percentage, potassium, MCV, hemoglobin, RBC, neutrophil percentage, monocyte percentage, and hematocrit.

Associations between hospital mortality and both hematological parameters and potassium

We then analyzed the associations between hospital mortality and both hematological parameters and potassium using logistic regression model. As shown in *Table 3*, in univariable analysis, all laboratory tests except neutrophil and monocyte percentages were associated with hospital mortality. However, in multivariable analysis, only SAPS I, MCHC, basophil, WBC and potassium were independently associated with hospital mortality.

Long-term prognostic values of hematological parameters and potassium

The long-term prognostic values of hematological parameters and potassium were analyzed using Cox regression model and the results were listed in *Table 4*. In univariable analysis, all laboratory tests except monocyte were significantly associated with long-term mortality. However, in multivariable analysis, only SAPS I, MCHC, RDW, WBC, lymphocyte percentage, potassium and neutrophil percentage were independently associated with long term mortality.

The subjects were then divided into five groups based on the MCHC and potassium, and the hospital mortality in all groups was shown in *Figure 1A*. Obviously, hospital mortality was significantly lower with the increase of MCHC. For potassium, hospital mortality was higher with the increase of potassium (i.e., potassium values >3.4 mmol/L). However, the subjects with potassium <3.3 mmol/L had higher hospital

Table 2 AUC of laboratory hematological parameter for predicting hospital mortality

Index tests	AUC	95% CI	P
SAPS I	0.752	0.727–0.776	<0.001
MCHC	0.650	0.622–0.677	<0.001
RDW	0.626	0.597–0.654	<0.001
Basophil	0.615	0.583–0.648	<0.001
WBC	0.611	0.580–0.641	<0.001
Lymphocyte	0.603	0.571–0.636	<0.001
Eosinophil	0.600	0.568–0.633	<0.001
Potassium	0.592	0.561–0.623	<0.001
MCV	0.580	0.550–0.610	<0.001
Hemoglobin	0.578	0.550–0.606	<0.001
RBC	0.570	0.541–0.599	<0.001
Neutrophil	0.554	0.520–0.589	0.001
Monocyte	0.548	0.513–0.582	0.004
Hematocrit	0.543	0.514–0.572	0.004

AUC, area under curve; CI, confidence interval; SAPS I, simplified acute physiology score I; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; WBC, white blood cell; MCV, mean corpuscular volume; RBC, red blood cell.

Table 3 Associations between potassium, hematological parameters and hospital mortality

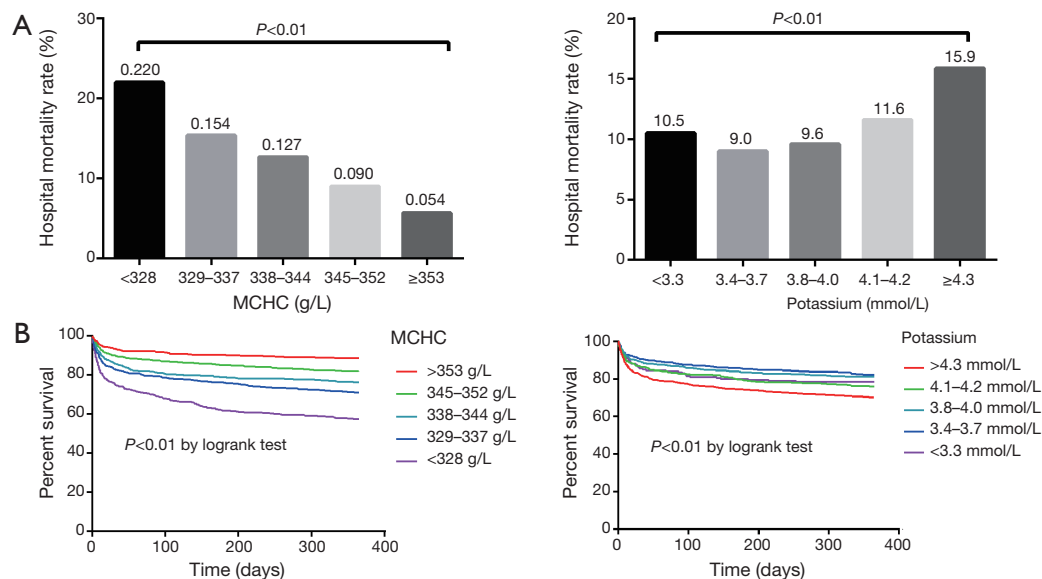
Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
SAPS I (per 5)	2.27 (2.05–2.52)	<0.001	2.00 (1.77–2.26)	<0.001
MCHC (per 10 g/L)	0.72 (0.67–0.77)	<0.001	0.84 (0.77–0.92)	<0.001
RDW (per 1%)	1.21 (1.15–1.28)	<0.001	–	–
Basophile (per 1%)	0.31 (0.20–0.49)	<0.001	0.50 (0.31–0.81)	0.005
WBC (per $5 \times 10^9/L$)	1.33 (1.23–1.44)	<0.001	1.13 (1.03–1.25)	0.009
Lymphocyte (per 5%)	0.89 (0.84–0.95)	<0.001	–	–
Eosinophil (per 1%)	0.88 (0.81–0.95)	0.002	–	–
Potassium (per mmol/L)	1.47 (1.31–1.65)	<0.001	1.17 (1.01–1.35)	0.031
MCV (per 5 fL)	1.28 (1.18–1.40)	<0.001	–	–
Hemoglobin (per 5 g/L)	0.59 (0.46–0.74)	<0.001	–	–
RBC (per $10^{12}/L$)	0.74 (0.64–0.86)	<0.001	–	–
Neutrophil (per 5%)	1.00 (0.96–1.05)	0.872	–	–
Monocyte (per 1%)	0.99 (0.95–1.03)	0.581	–	–
Hematocrit (per 5%)	0.91 (0.83–0.99)	0.030	–	–
Age (per 5 years)	1.05 (1.03–1.07)	<0.001	–	–

OR, odds ratio; CI, confidence interval; –, no data available; SAPS I, simplified acute physiology score I; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; WBC, white blood cell; MCV, mean corpuscular volume; RBC, red blood cell.

Table 4 Association between both hematological parameters and potassium and one year mortality

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
SAPS I (per 5)	1.74 (1.64–1.85)	<0.001	1.52 (1.41–1.63)	<0.001
MCHC (per 10 g/L)	0.72 (0.69–0.75)	<0.001	0.84 (0.80–0.89)	<0.001
RDW (per 1%)	1.21 (1.18–1.25)	<0.001	1.06 (1.02–1.11)	0.005
Basophil (per 1%)	0.54 (0.41–0.70)	<0.001	–	–
WBC (per $5 \times 10^9/L$)	1.18 (1.13–1.23)	<0.001	1.06 (1.00–1.13)	0.040
Lymphocyte (per 5%)	0.87 (0.83–0.91)	<0.001	0.83 (0.78–0.89)	<0.001
Eosinophil (per 1%)	0.92 (0.88–0.97)	0.002	–	–
Potassium (per mmol/L)	1.37 (1.28–1.47)	<0.001	1.15 (1.06–1.25)	0.001
MCV (per 5 fL)	1.03 (1.02–1.04)	<0.001	–	–
Hemoglobin (per 5 g/L)	0.47 (0.40–0.54)	<0.001	–	–
RBC (per $10^{12}/L$)	0.67 (0.62–0.74)	<0.001	–	–
Neutrophil (per 5%)	1.03 (1.00–1.07)	0.041	0.91 (0.87–0.96)	0.001
Monocyte (per 1%)	0.99 (0.97–1.03)	0.938	–	–
Hematocrit (per 5%)	0.82 (0.78–0.87)	<0.001	–	–
Age (per 5 years)	1.04 (1.03–1.05)	<0.001	–	–

HR, hazard ration; CI, confidence interval; –, no data available; SAPS I, simplified acute physiology score I; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; WBC, white blood cell; MCV, mean corpuscular volume; RBC, red blood cell.

**Figure 1** Prognostic values of MCHC and potassium. MCHC, mean corpuscular hemoglobin concentration.

mortality than those with potassium between 3.4 and 4.0 mmol/L, indicating that there may be a U-shape (or J-shape) relationship between hospital mortality and potassium. *Figure 1B* is Kaplan-Meier curves depicting the prognostic values of MCHC and potassium. Subjects with higher MCHC had significantly lower mortality risk ($P < 0.01$ by log-rank test). When potassium was > 3.4 mmol/L, higher mortality risk was observed, and subjects with potassium < 3.3 mmol/L also had higher mortality risk.

Discussion

In this study, we investigated the prognostic values of hematological parameters and serum ion levels in adult AMI patients admitted to ICU. Some findings in our study were consistent with previous investigations. Specifically, increased RDW (4) and WBC (8) were found to be associated with poorer outcomes after AMI. However, our study has two strengths: firstly, to the best of our knowledge, this is the first study that investigated the prognostic values of these laboratory tests simultaneously, so that the confounding effects of these laboratory tests on AMI outcomes could be minimized. Therefore, the results of our study may be more reliable than previous investigations. Second, for the first time, we found that decreased MCHC was independently associated with poorer prognosis, either indicated by hospital mortality or 1-year mortality of AMI.

We compared the clinical characteristics of hospital survivors and non-survivors, and found that some of laboratory tests were associated with hospital outcomes, such as RDW and potassium. These findings are partially consistent with previous reports (4-11). However, we noted that percentages of basophil and eosinophil were decreased in hospital non-survivors, suggesting that eosinophil and basophil percentages are potential prognostic factors for AMI and thus unmasking a potential (new) of these blood cells in the complications of acute coronary syndrome. Indeed, using ROC curve analysis, we found that the AUC of basophil and eosinophil for predicting hospital mortality were approximately 0.60, which are comparable to those of WBC and RDW, two well-recognized prognostic factors in AMI. To our knowledge, this is the first study reported that eosinophil and basophil are prognostic factors for AMI. Jiang *et al.* (20) found that eosinophil percentage was inversely correlated with cardiac troponin I level in AMI. Although that study suggested that eosinophil percentage was a potential prognostic factor, the prognostic value of eosinophil percentage was not further investigated.

We believe that decreased eosinophil percentage in AMI patients may be attributed to the following reasons. Firstly, AMI is an inflammatory related disease, which may increase neutrophil percentage, and therefore, eosinophil percentage is decreased (21,22). Second, during the development of AMI, cortisol level is increased (23), which can decrease the peripheral eosinophil percentage (24,25), as also noticed in additional studies investigating the acute behavior of eosinophils in stress conditions (26). Although we failed to find the independent prognostic value of eosinophil for AMI, this may be due to the small sample size of our study, and we believe that further studies with large sample sizes may be needed to investigate the prognostic value of eosinophil percentage in patients with this condition.

The most novel and important finding of our study is that increased MCHC is independently associated with decreased hospital and 1-year mortality. The mechanisms under increased MCHC and better outcomes of AMI patients are largely unknown. MCHC is defined as the average hemoglobin level in a RBC. We hypothesized that inflammation and iron status may partially explain the association between increased MCHC and poorer outcomes in AMI patients. It is widely-accepted that inflammatory response plays a crucial role in the occurrence and development of AMI (27,28). Increased inflammatory markers, such as CRP, predict poor prognosis of AMI (29,30), and anti-inflammatory agents such as corticosteroid can decrease mortality in AMI patients (31). Inflammatory response may lead to iron deficiency (32,33), which decrease MCHC (34). Therefore, similar to RDW (35), MCHC can be regarded as an inflammatory marker and thus can affect the prognosis after AMI. Our hypothesis was supported by a recently published work, which shown that MCHC was negatively correlated with RDW in AMI patients (36). Actually, higher serum iron was proved to be associated with better outcomes in AMI patients (37).

Our study has some limitations. Firstly, this is a retrospective analysis; therefore, subject selection bias cannot be ignored. Second, since some of the prognostic factors, such as cardiac troponin, in some patients were not available in MIMIC II, we could not investigate whether the prognostic value of MCHC was independent of these prognostic factors. Finally, it should be noted that the subjects enrolled in this study were admitted to ICU, thus conclusions of this study cannot be extended to the AMI patients admitted to other departments, such as cardiology department or emergency department.

In conclusion, we found that hematological parameters

and serum potassium can provide prognostic information in AMI patients. MCHC was an independent prognostic factor for both short and long term outcomes of AMI.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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