


The relationship of the hemoglobin to serum creatinine ratio with long-term mortality in patients with acute coronary syndrome

A retrospective study

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Abstract

Acute coronary syndrome (ACS) is an urgent clinical condition of cardiovascular diseases. The present study evaluated the predictive efficacy of the hemoglobin to serum creatinine ratio (Hgb/Cr) on long-term mortality in patients with ACS. The ratio, representing the proportion of the 2 values, is cheap, practical, and very easy to calculate at the bedside. Our study included 475 patients who were admitted to the coronary intensive care unit with a diagnosis of ACS and who underwent coronary angiography. The Hgb/Cr ratio was calculated by dividing the admission hemoglobin by the admission serum creatinine. All patient data were collected from the electronic hospital information system, patient files, and the hospital's archive. A comparison of the patients laboratory findings revealed that the Hgb/Cr ratios differed significantly between the survivor and non-survivor group [16.6 (7.7–49) vs 13.8 (4.91–32.8), respectively; $P < .001$]. A univariate Cox regression analysis showed that the Hgb/Cr ratio was statistically significant in predicting long-term mortality (0.836; 95% confidence interval [CI]: 0.781–0.895; $P < .001$). After adjusting the model by adding clinically and statistically significant variables, the Hgb/Cr ratio was still an independent predictor of long-term mortality (0.886; 95% CI: 0.815–0.963; $P = .004$). The Hgb/Cr ratio's discriminant ability was tested with an receiver operating characteristic curve analysis. The Hgb/Cr ratio's area under the curve value was 0.679 (95% CI: 0.609–0.750; $P < .001$). A survival analysis using the Kaplan–Meier curve of the 2 Hgb/Cr ratio groups (according to cutoff value) revealed that the low-Hgb/Cr group had a significantly higher mortality rate than high-Hgb/Cr group. The Hgb/Cr ratio was found to be an independent predictor of long-term mortality in ACS patients.

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, CI = confidence intervals, CKD = chronic kidney disease, DM = diabetes mellitus, EPO = erythropoietin, GFR = glomerular filtration rate, Hgb/Cr = hemoglobin to-serum creatinine ratio, HT = hypertension, LDL = low density lipoprotein, NONSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction.

Keywords: anemia, creatinine, hemoglobin, hemoglobin to creatinine ratio, mortality

1. Introduction

Acute coronary syndrome (ACS) is an urgent clinical condition of cardiovascular diseases, embracing ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NONSTEMI), and unstable angina. According to 2021 data from the American Heart Association, 805,000 people experience ACS in the United States annually, including 605,000 new and 200,000 recurrent attacks.^[1,2]

Many scorings and risk assessment algorithms have been developed to predict and reduce the mortality of coronary artery disease (CAD). The evaluated values of scores such as Killip and Pursuit in ACS patients were identified entirely by

clinical findings, whereas scores such as GRACE and CRUSADE were further supported by laboratory findings.^[3–6] Both hemoglobin and serum creatinine are parameters used in CAD scoring and algorithms.

Anemia, defined as a reduction of the red blood cells that are responsible for tissue oxygenation, is a disease that increases the heart's workload due to cardiovascular compensation. In a review by Guedeny et al^[7] that analyzed 15 studies, anemia was found to be 10.5% to 46.4% more common in patients with ACS.^[8]

The other parameter, serum creatinine, is a laboratory finding used in the diagnosis and follow-up of chronic kidney disease

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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(CKD) in clinical practice. The frequency of chronic kidney injury which is known to increase cardiovascular events for many reasons, such as chronic inflammation, oxidative stress, endothelial dysfunction, and calcification increases up to 20%-25% in ACS patients.^[9,10]

As suggested by these findings, CAD is often accompanied by anemia and impaired renal function. This association, which is frequently seen in patients with ACS, has been evaluated in studies, and a relationship has been shown of anemia and impaired renal function with increased early and long-term mortality and adverse outcomes in patients with ACS.^[7,11–15]

Hemoglobin and serum creatinine are 2 simple parameters that are routinely evaluated in patients presenting with ACS. The hemoglobin to serum creatinine ratio (Hgb/Cr) ratio, representing the proportion of the 2 values, is cheap, practical, and easy calculate at the bedside. Our study evaluated the predictive effect of Hgb/Cr ratio on long-term mortality in patients with ACS.

2. Materials and methods

2.1. Patients

Using a hospital electronic data information system and patient files, this cross-sectional study retrospectively analyzed 529 patients who were diagnosed with ACS by a cardiologist, were hospitalized in coronary intensive care, and underwent coronary angiography from January 2015 through January 2018. STEMI and NONSTEMI patients aged 18 to 90 years were included in the study. Fifty-four patients were excluded who had active malignancy, severe hepatic and renal failure (typically a serum creatinine > 2.0 mg/dL), active or recent internal bleeding, known bleeding diathesis, or other significant comorbidities as well as patients who died in hospital or received erythrocyte transfusion upon hospitalization (Fig. 1).

2.2. Data collection

We analyzed the patients' peripheral venous blood samples in the hematology laboratory, and complete blood count parameters were calculated by an automated blood counter

(Beckman Coulter, Brea, CA). Urea, creatinine, glomerular filtration rate (GFR), albumin, alanine aminotransferase, total cholesterol, high-density lipoprotein, low-density lipoprotein (LDL), total protein, troponin I, and blood glucose levels were analyzed in the biochemistry laboratory for all patients upon admission.

The patients demographic characteristics and clinical and laboratory data were recorded. Medical treatments, echocardiographic and angiographic findings, and in hospital and long-term endpoints were collected from the electronic hospital information system, patient files, and the hospital's archive. The patients date-of-death information was obtained via the hospital data system.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Non-interventional Clinical Research Ethics Committee, decision no. 2023/07-27).

2.3. Statistical analysis

We analyzed the data using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY). The parametric data are presented as mean \pm 6 standard deviations and as medians (minimum to maximum) as appropriate. The categorical variables are shown as numbers and percentages. The differences among the categorical variables of the groups were analyzed using the chi-squared test. The normality of distribution was investigated with the Shapiro–Wilk test for parametric data, and the homogeneity of the data was analyzed using Levene test. The differences in the numerical variables for the independent groups were analyzed with either the *t* test or the Mann–Whitney *U* test. The discriminant abilities and cutoff points of the Hgb/Cr ratio in predicting long-term mortality were compared using the area under the receiver operating characteristic.

The survival analysis was done using the Kaplan–Meier product limit estimate method according to cutoff value. Univariate and multivariate Cox regression models were used to evaluate the independent association of the Hgb/Cr ratio with long-term mortality; the unadjusted and adjusted hazard ratios are reported with their respective 95% confidence intervals (CIs). Clinically and statistically significant variables were also included in the variants in the Cox regression analysis. The level of significance was set at $P < .05$.

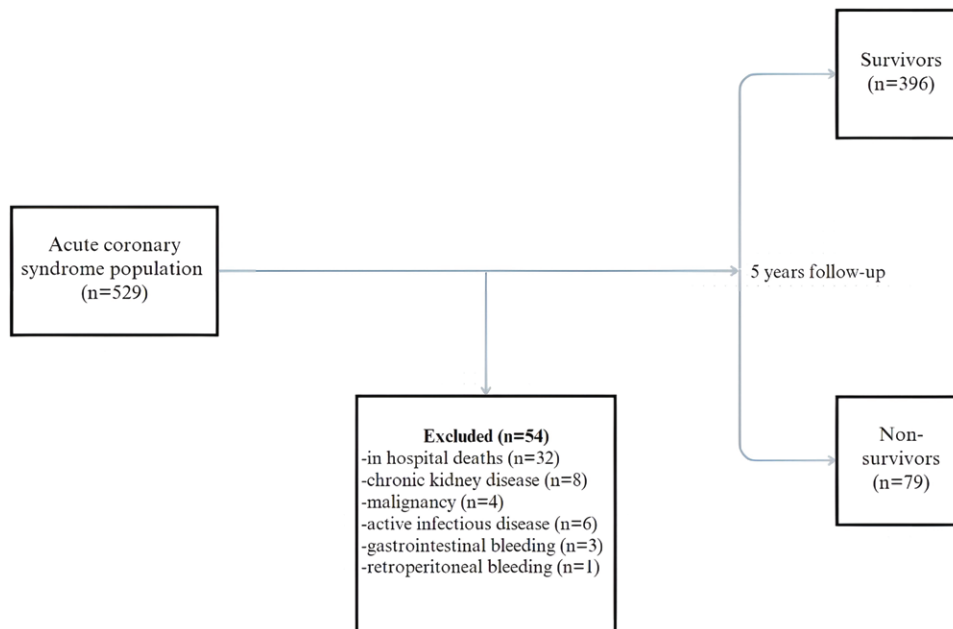


Figure 1. Diagram of the patient flowchart.

Table 1**Baseline characteristics of the acute coronary syndrome population according to survival.**

Characteristics	Survivors (n = 396)	Non-survivors (n = 79)	P value
Age (yr), mean ± SD	57.2 ± 11.9	70.4 ± 12.8	<.0001
Sex, female %	24	41.8	.001
Diabetes mellitus, %	27.3	34.2	.214
Hypertension, %	29.8	43	.021
Prior cerebrovascular event, %	2	7.6	.017
Peripheral artery disease, %	0.8	3.8	.061
MI type (STEMI), %	58.1	50.6	.870
Antiaggregants, %	98	89.9	.002
Beta-blockers, %	48.7	45.6	.607
ACE inhibitors- ARB, %	72.7	70.9	.738
Statins, %	58.1	44.3	.024
Ejection fraction (%), median (min–max)	50.4 (20–70)	44 (15–68)	<.001
Blood glucose (mg/dL), median (min–max)	154 (57–453)	185.4 (83–452)	.011
Serum creatinine (mg/dL), median (min–max)	0.91 (0.25–1.56)	1.02 (0.5–1.94)	.001
Total cholesterol (mg/dL), median (min–max)	184 (87–402)	180.4 (82–299)	.558
LDL-C(mg/dL), median (min–max)	114.2 (21.20–330)	115.7 (37–221)	.780
HDL-C (mg/dL), median (min–max)	38.6 (5–85)	38.9 (18–68)	.790
Triglyceride (mg/dL), median (min–max)	156.6 (11–896)	127.7 (36–381)	.004
WBC (×10 ³ µL), median (min–max)	11 (4.1–26.9)	11.5 (4.7–22.4)	.311
Hemoglobin (g/dL), median (min–max)	14.2 (8.1–18.3)	13.1 (8.5–17.2)	<.001
Platelet (×10 ³ µL), median (min–max)	235.4 (56–566)	247.2 (64–542)	.227
Neutrophyl (×10 ³ µL), median (min–max)	7.9 (2.2–23.4)	8.7 (0.4–20.4)	.099
ALT (U/L), median (min–max)	29.9 (9–369)	26.7 (7–116)	.358
Albumin (g/L), median (min–max)	40.6 (20–52.6)	39.2 (28–47.7)	.088
Troponin (ng/mL), median (min–max)	9837 (0.17–99,000)	8508 (0.20–94,000)	.625
Hgb/Cr ratio, median (min–max)	16.6 (7.7–49)	13.8 (4.91–32.8)	<.001

ACE = angiotensin-converting enzyme, ALT = alanine aminotransferase, ARB = angiotensin receptor blocker, HDL-C = high-density lipoprotein-cholesterol, Hgb/Cr = hemoglobin to-serum creatinine ratio, LDL-C = low density lipoprotein-cholesterol, MI = myocardial infarction, STEMI = ST elevated myocardial infarction, WBC = white blood cell.

Table 2**Unadjusted and adjusted Cox proportional hazards model for post-acute coronary syndrome 5 year all-cause mortality.**

Variables	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.082 (1.061–1.102)	<.001	1.062 (1.037–1.088)	<.001
Gender	0.481 (0.308–0.753)	.001	NS	NS
HT	1.707 (1.093–2.665)	.019	NS	NS
DM	1.329 (0.835–2.116)	.230	NS	NS
Prior CVE	3.556 (1.545–8.182)	.003	NS	NS
LDL-cholesterol	1.001 (0.995–1.006)	.749	NS	NS
Ejection fraction	0.955 (0.935–0.975)	<.001	0.960 (0.938–0.983)	.001
Antiaggregants	0.229 (0.110–0.477)	<.001	NS	NS
Statins	0.592 (0.380–0.923)	.021	NS	NS
Hgb/Cr ratio	0.836 (0.781–0.895)	<.001	0.886 (0.815–0.963)	.004

CVE = cerebrovascular event, DM = diabetes mellitus, Hgb/Cr = Hemoglobin to-serum creatinine ratio, HT = hypertension, LDL = low density lipoprotein.

3. Results

Our study included 475 patients, 128 (27%) women and 347 (73%) men, who were hospitalized with a diagnosis of ACS and underwent coronary angiography. The mean age was 59.4 ± 13 years, and the mean follow-up period was 53.8 ± 16.3 months. It was observed that 79 (16.6%) of the patients died during follow-up. The patients were divided into 2 groups as survivors and non-survivors.

Age was higher in non-survivors than in survivors (70.4 ± 12.8 years vs 57.2 ± 11.9 years, respectively; $P < .001$), also ejection fraction was lower [44 (15–68) vs 50.4 (20–70), respectively; $P < .001$]. It was observed that female gender (24.2% vs 41.8%; $P = .001$), history of hypertension (HT) (29.8% vs 43%; $P = .021$), and history of cerebrovascular

event (2% vs 7.6%; $P = .017$) were significantly associated with mortality. When the medications of the patients were compared, it was found that statin (44.3% vs 58.1%; $P = .024$) and antiaggregant therapy (89.9% vs 98%; $P = .002$) usage rates were significantly lower in non-survivors. A comparison of the patients laboratory findings revealed that hemoglobin [14.2 (8.1–18.3) vs 13.1 (8.5–17.2); $P < .001$], serum creatinine [0.91 (0.25–1.56) vs 1.02 (0.5–1.94); $P = .001$], blood glucose [154 (57–453) vs 185.4 (83–452); $P = .011$] values and Hgb/Cr ratios [16.6 (7.7–49) vs 13.8 (4.91–32.8); $P < .001$] differed significantly between the survivor and non-survivor group, respectively. Table 1 shows the baseline clinical, demographic, and laboratory characteristics of the study population according to survival status. There were no significant differences in myocardial infarction (MI) type, lipid profile, white blood cell, platelet, or troponin parameters between the survivor and non-survivor upon admission.

According to the univariate Cox regression analysis, the Hgb/Cr ratio was statistically significant in predicting long-term mortality (0.836; 95% CI: 0.781–0.895; $P < .001$). After adjusting the model by adding clinically and statistically significant variables (age, gender, ejection fraction, HT, history of diabetes mellitus [DM], cerebrovascular event, LDL, statin, and antiaggregant use), the Hgb/Cr ratio remained an independent predictor of long-term mortality (0.886; 95% CI: 0.815–0.963; $P = .004$) (Table 2).

The Hgb/Cr ratio's discriminant ability was tested with receiver operating characteristic curve analysis. The Hgb/Cr ratio's area under the curve value was 0.679 (95% CI: 0.609–0.750; $P < .001$). The cutoff value of the Hgb/Cr ratio was 14.86, with a sensitivity of 63.7% and a specificity of 64.1% (Fig. 2).

A survival analysis of the 2 Hgb/Cr ratio groups (according to cutoff value) using the Kaplan–Meier curve revealed that the low-Hgb/Cr group had a significantly higher mortality rate than the high-Hgb/Cr group (Fig. 3).

4. Discussion

Our study demonstrated the effect of Hgb/Cr ratio on long-term mortality in patients with ACS, defined as a sudden decrease in blood flow to the heart that is often caused by rupture of the lipid-burden coronary artery plaque followed by platelet aggregation and coronary artery obstruction.^[1,16] The most important risk factors for ACS have been identified as age, smoking, DM, HT, hyperlipidemia, and body mass index. The incidence of CAD patients is expected to increase in the future due to obesity,

unhealthy lifestyles, and especially the aging population.^[1,17] In the past century, the average survival rate in patients with ACS has improved with the increase in medical treatment agents that have demonstrated an effect on mortality in CAD and with the advance of percutaneous intervention methods. However, CAD still accounts for about 1-3rd of all deaths worldwide.^[17] Many blood parameters have shown an association with mortality in ACS patients, including high blood sugar at admission, increased troponin levels, increased inflammatory markers, low hemoglobin level, and increased serum creatinine level.^[18-20]

Anemia is defined as a decrease in red blood cells and is evaluated by a decrease in hemoglobin in clinical practice. It is common both in the general population and in CAD patients and is a disease with a multifactorial etiology. Anemia, which various randomized studies have found to be present in 10% to 43% of ACS patients, is associated with poor prognosis in both the early and late periods of ACS.^[21,22]

Anemia in ACS patients may predate hospitalization or develop during or after hospitalization. Anemia in CAD patients is typically normocytic, normochromic, and hypo-proliferative,^[22] and it can have many causes. Although a slight increase in erythropoietin (EPO) levels has been observed in CAD patients, it remains quite low compared to anemia levels.^[22-24] In addition, about 10% to 20% of these patients have erythropoietin stimulating agent resistance, and decreased EPO levels may also lead to a decrease in the cardioprotective effects of EPO.^[21-24]

Other important causes of anemia include the hemodilution observed in heart failure patients and the use of antiaggregants and anticoagulants in ACS patients. Especially in the elderly ACS population, nutritional deficiencies, such as iron, b12, and folic acid, often play a more prominent role in the etiology of anemia.^[21,25] Because anemic patients are often older and often use insufficient antiaggregant or anticoagulants, patient profile also has a negative impact on prognosis.^[21,26]

Furthermore, inflammatory cytokines that occur in ACS patients, such as IL-1, IL 6, and TNF α , affect anemia through the inflammatory response by decreasing the red blood cells half-life, lowering the EPO level and reducing iron bioavailability. The anemia of chronic disease can also be seen in ACS

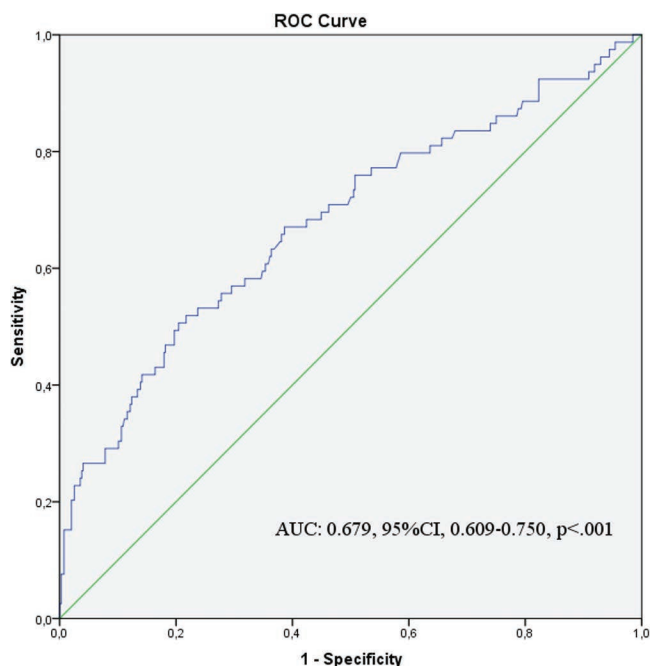


Figure 2. Receiver–operating characteristic (ROC) curve analysis plot to determine the cutoff value of Hgb/Cr ratio in the prediction of mortality.

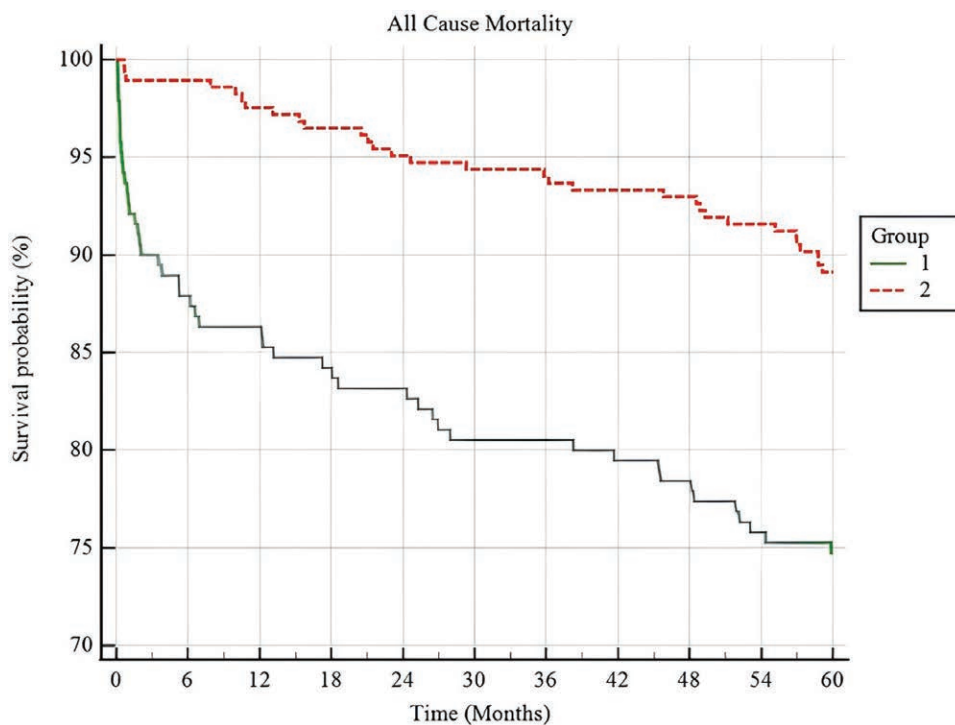


Figure 3. Kaplan–Meier survival curves of 5-year mortality post-ACS according to Hgb/Cr ratio groups. ACS = acute coronary syndrome.

through the same pathways.^[21,27] Anemia leads to a decrease in myocardial oxygen supply, exacerbation of ischemia, and formation of myocardial necrosis and fibrosis, ultimately adversely affecting prognosis in patients with CAD.^[12,21]

The Myocardial Ischemia National Audit Project registry published by Mamas et al^[28] evaluated the relationship between anemia and mortality in patients with ACS. Anemia was found to be independently associated with 30-day and 1-year mortality in ACS patients, and a significant correlation was observed between hemoglobin levels and death outcomes. A review by Sabatine et al^[12] analyzed about 40,000 patients included in 16 clinical ACS studies to compare the levels of anemia and cardiovascular outcomes. It found that hemoglobin under 14 mg/dL in STEMI patients significantly and progressively increased cardiovascular mortality and congestive heart failure, while hemoglobin under 11 mg/dL in NONSTEMI patients also showed an independent relationship with death, MI, and recurrent ischemia. In a study involving 936 patients, female patients with suspected ischemia were compared to evaluate anemia and adverse cardiovascular outcomes. Anemia was identified as an independent predictor of adverse cardiovascular outcomes, with the risk increasing by 20% for each 1 g/dL reduction in hemoglobin.^[29]

Serum creatinine concentration, a common measure of glomerular filtration rate, is a clinical indicator of kidney function.^[10] Age, DM, HT, and smoking, which are risk factors for CAD, are also risk factors for CKD. Additionally, CKD has been identified as a major risk factor for CAD.^[2,3,30]

When prospective studies of chronic kidney patients are evaluated, cardiac events and increased incidence of CAD can be explained by changes in fibrinogen and homocysteine metabolism, increased lipoprotein (a) levels, hypoalbuminemia, increased inflammatory mediators, increased oxidized LDL, high-density lipoprotein dysfunction, the development of micro- and macrocalcification in coroner arteries, and decreased plaque stabilization.^[30-32] Intimal calcification, which leads to a high frequency of cardiac events, is more common in patients with advanced CKD, but medial calcification due to a longer hemodialysis time and serum calcium phosphate abnormalities is a more common finding in patients of younger age.^[33,34] The extent of coronary arterial calcification in CKD patients has been associated with a greater coronary plaque burden compared to the general population. In addition, the chronic inflammatory process in CKD patients, the inhibition of nitrite oxide synthesis, and uremic myocardial damage without coronary stenosis are other leading causes of adverse cardiovascular events in these patients.^[34]

Factors that may affect the prognosis of CAD patients with CKD include a delay in diagnosis due to atypical findings, the defensive approach that is occasionally taken due to concerns about contrast nephropathy in invasive procedures, and the insufficient use of drugs such as antiplatelets, angiotensin-converting enzyme inhibitors, etc.^[35]

There are many studies on the negative prognostic effect of impaired renal function in patients with ACS.^[36] An article by Reddan et al^[37] analyzed 13,707 ACS patients from 2 clinical studies and found that every 10 mL increase in GFR reduced mortality in these patients. Another study, the Valsartan in Acute Myocardial Infarction Trial (VALIANT), included 14,527 ACS patients and found that every 10-unit reduction in estimated GFR was associated with an increased risk ratio (1:10) for death and nonfatal cardiovascular outcomes.^[38] A study by Qi et al^[35] included 1840 patients who were categorized and compared in 3 groups as GFR > 90, GFR 60 to 90, and GFR < 60. A low GFR was associated with an unfavorable prognosis and high mortality.

In Numasawa et al^[39] comprehensive a Japanese Nationwide Registry study, the relationship between hemoglobin creatinine ratio, a new parameter, and in hospital mortality was evaluated

in 157,978 patients who did not undergo dialysis but underwent percutaneous coronary intervention. It found that the Hgb/Cr ratio was independently associated with both in hospital mortality and bleeding complications. A study by Çamcı et al^[40] compared contrast nephropathy and Hgb/Cr in 500 patients who underwent percutaneous coronary intervention and found that the Hgb/Cr ratio is also an independent predictor of contrast nephropathy.

ACS is a clinical condition with high early and late mortality. The aim of treatment in these patients is to reduce mortality in the late as well as the early period, so it is crucial to conduct risk assessment in these patients starting from diagnosis. In this respect, the ratio of hemoglobin and serum creatinine, which are routinely evaluated in each patient, can provide additional information for risk scoring as a simple, easily calculated bedside evaluable parameter. In patients with CAD, who are often more anemic, older, and have higher rates of inadequate treatment due to impaired renal function, such an assessment can inform the planning of closer follow-up and the selection of more intensive treatment strategies for those with a higher risk of mortality.

5. Limitations

This study has several limitations. First, the study was designed as a retrospective study. Second, our number of patients is inadequate, so there is a need for studies with a larger number of patients. Third, we did not have accurate data on the individual etiology of anemia and CKD in patients with low hemoglobin and high creatinine levels. Fourth limitation of the study is that the discharge hemoglobin and serum creatinine parameters of the patients are not routinely checked and their data are incomplete, and they are not included in the study due to the lack of follow-up data. The last, there were insufficient data on whether individual CAD and heart failure treatment were optimal.

6. Conclusion

The Hgb/Cr ratio was found to be an independent predictor of long-term mortality in ACS patients. The Hgb/Cr ratio is a simple, inexpensive bedside index and appears to be successful in mortality scoring or risk assessment. It can be widely used in daily practice in the near future with the support of prospective studies with larger patient numbers.

Author contributions

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