Association Between Nadir Hematocrit and Severe Acute Kidney Injury After Off-Pump Coronary Artery Bypass Graft Surgery: A Retrospective Cohort Study Based on the MIMIC-IV Database

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Background: We aimed to evaluate the association between postoperative nadir hematocrit (Hct) and severe acute kidney injury (AKI) in patients undergoing off-pump coronary artery bypass graft (OPCABG) surgery.

Material/Methods: Data of patients who received OPCABG were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. A generalized additive model was applied to explore the relationship between nadir Hct and severe AKI. Patients were divided into 4 groups by quartiles of postoperative nadir Hct, with the lowest group (Hct <25%) as reference. We conducted multivariate logistic regression models to calculate adjusted odds ratios (OR) and 95% CI and evaluate trend among the 4 groups.

Results: In total, 1783 OPCABG patients were included. A nonlinear association between nadir Hct and severe AKI was identified. After adjusting for potential confounders, nadir Hct was negatively associated with risk of severe AKI when Hct was less than 31%; there was no statistical significance between highest Hct group (Hct ≥31%) and control group (Hct <25%; P>0.05). Tests for trend were significant (P<0.05). Subgroup analyses showed each 1% increase in postoperative nadir Hct was associated with a 23% decrease in risk of severe AKI (OR, 0.77; P=0.002) in lower BMI group (<30 kg/m²).

Conclusions: The association between postoperative nadir Hct and severe AKI in patients after OPCABG was nonlinear. Lower nadir Hct may be associated with increased risk of severe AKI when Hct values are less than 31%. However, no statistical significance was found between the highest Hct group and control group.

Keywords: Acute Kidney Injury • Coronary Artery Bypass, Off-Pump • Hematocrit

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Background

Coronary heart disease has become a global health problem, and coronary artery bypass graft (CABG) surgery remains a critical treatment. Acute kidney injury (AKI) is one of the most common complications following CABG. It was reported that approximately 30% of patients who underwent CABG developed AKI, and up to 2% of the patients needed postoperative renal replacement therapy [1,2]. Patients who develop severe AKI tend to have increased morbidity, prolonged hospital stay, and long-term adverse outcomes [3-5]. Cardiopulmonary bypass (CPB) could help to construct a still field in the anastomosis operation. However, lower nadir hematocrit (Hct) during CPB is associated not only with the risk of severe AKI, but also with a higher risk of myocardial injury and mortality [6-8]. Off-pump coronary artery bypass graft (OPCABG) surgery, while avoiding CPB, could decrease the operative risk in patients with high preoperative risk scores [9]. However, few studies have clarified the association between nadir Hct and the risk of severe AKI after OPCABG. To date, there has been no clear consensus on the optimal range of Hct level after OPCABG.

We aimed to assess the relationship between the nadir Hct and severe AKI after OPCABG, defined as stage III according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [10].

Material and Methods

Ethics Statement

The establishment of the Medical Information Mart for Intensive Care IV (MIMIC-IV) database was approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology (Cambridge, MA, USA), and consent was obtained for the original data collection. Therefore, the ethics approval statement and the need for informed consent were waived for the studies on this database.

Database Source

We extracted data from the MIMIC-IV database, a publicly available clinical database with over 250,000 admissions at Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2008 to 2019 [11]. One author (Yisen Deng) gained access to the database after passing the Collaborative Institutional Training Initiative examination (certification no: 10261850).

Inclusion and Exclusion Criteria

Structured Query Language (SQL) with Navicat (version 15.0.26) was used to extract all the necessary data. We included patients who underwent the CABG procedure using the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes. The original data collected included demographic characteristics, comorbidities, vital signs, laboratory outcomes, clinical scoring systems, and vasopressor use. Baseline features were recorded within 24 h after Intensive Care Unit (ICU) admission. Patients who underwent CABG surgery were screened initially. The exclusion criteria were as follows: (1) patient received on-pump coronary artery bypass graft (ONCABG) surgery; (2) patient had chronic renal disease; (3) length of ICU stay was <1 day; (4) patient was transferred to ICU before ONCABG or 1 day after surgery; (5) KDIGO stage or primary data were missing.

Management of Missing Data

Albumin, bilirubin, and calcium levels and other variables with more than 15% of their values missing were removed from our analysis. For variables with approximately 7% of values missing (temperature and height), we replaced the missing values with median values.

Outcome Definition

The outcome of our study was severe acute kidney injury (AKI), defined as stage III AKI according to KDIGO criteria.

Statistical Analysis

As appropriate, continuous variables were characterized as the mean±standard deviation (SD) or medians (interquartile range, IQR). Categorical data were expressed as counts and percentages. First, we conducted a generalized additive model to explore the relationship between nadir Hct and severe AKI. Then, the patients were divided into 4 groups according to quartiles of postoperative nadir Hct, and the lowest Hct group (Hct <25%) was used as a reference (control). We used one-way ANOVA (gaussian-distribution and continuous variables), Kruskal-Wallis H (abnormal-distribution and continuous variables), and chi-square tests (categorical variables) to analyze baseline characteristics. To explore the association between postoperative nadir Hct and risk of severe AKI, unadjusted and adjusted multivariate logistic regression models were used to compare each Hct group with the reference, and the trends of Hct among the 4 groups were evaluated. Subgroup analysis was also used to evaluate the modification effects on the relationship between nadir Hct and severe AKI through stratified logistic regression models. All the tests in this study were 2-tailed, and a P value less than 0.05 was considered statistically significant. All analyses were conducted with the statistical software package R (http://www.R-project.org) and Free Statistics software version 1.3 [12].
Results

We identified 256,878 patients in the MIMIC-IV database. Among these, 250,959 patients did not undergo CABG. Among the excluded patients, 571 were transferred to the ICU before ONCABG or 1 day after surgery, 2,909 received ONCABG, 501 had chronic renal disease, 85 stayed in the ICU less than 1 day, 60 had KDIGO stage data missing, and 10 had primary data missing. Consequently, 1,783 patients were included in our analysis after screening step by step (Figure 1). The patients were divided into 4 groups according to quartiles of postoperative nadir Hct. The mean (SD) age of the patients was 67.8±9.9 years old, and 21.5% were female. Patients with lower levels of hematocrit (<25%) had a high rate of congestive heart failure, peripheral vascular disease, cerebrovascular disease, and rheumatic disease. Patients with higher levels of hematocrit (≥31%) tended to have higher body mass index (BMI), diastolic blood pressure, white blood cell (WBC) count, and hemoglobin and bicarbonate levels. In addition, higher sequential organ failure assessment (SOFA) scores, simplified acute physiology score II (SAPSII), and vasopressor use were observed in the low-hematocrit group (<25%) than in the high-hematocrit group (≥31%) (Table 1).

A nonlinear association between postoperative nadir Hct and severe AKI in patients who received OPCABG was observed in the generalized additive model. Nadir Hct was found to be negatively associated with the risk of severe AKI when the Hct value was less than 31%. Additionally, nadir Hct tended to be positively associated with the risk of severe AKI when the Hct value was more than 31% (Figure 2). To further identify the association between nadir Hct and severe AKI, multivariate logistic regression models were conducted using the low Hct group as a reference. In model I, a decreased risk of severe AKI was observed in the higher Hct group than in the low Hct level group (Hct <25%), after adjusting for age and sex. In model II, similar results were observed after adjusting for age, sex, BMI, myocardial infarction, congestive heart failure, peripheral vascular disease, rheumatic disease, diabetes with or without complications, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, glucose, pulse oxygen saturation (SpO2), WBC, platelets, anion gap, lactate, bicarbonate, chloride, sodium, potassium, activated partial thromboplastin time (APTT), SOFA, SAPSII, vasopressin, epinephrine, norepinephrine, and phenylephrine. Eventually, we found that the higher nadir Hct groups were associated with a decreased risk of severe AKI when the Hct value was less than 31%, after it was adjusted for the potential confounders. The tests for trend were statistically significant when we entered the median value of each group as a continuous variable (P<0.05). However, we found no statistical significance in the highest Hct group compared with the control group (Table 2).

Discussions

AKI is a well-recognized complication for patients undergoing cardiac surgery and can notably affect short-term and long-term prognoses [5]. Patients who develop postoperative AKI have a lower survival rate than patients without AKI, even if they develop mild AKI or recover after proper treatment [13,14]. Prior studies have pointed out that nadir Hct is associated with poorer renal function, more myocardial injury, extended hospital stay, and higher mortality in patients who undergo ONCABG [3,5,6,15]. Although it is known that the degree of hemodilution during CPB is associated with postoperative AKI, which requires dialysis support [16], few studies have explored the relationship between postoperative Hct levels and AKI. Moreover, the optimal range of Hct after OPCABG remains to be clarified. In this retrospective study, we found a nonlinear association between postoperative nadir Hct and severe AKI in patients who underwent OPCABG. Lower nadir Hct was associated with increased risk of severe AKI when the Hct value was less than 31%. In the subgroup analysis, we observed a potential interaction between BMI and nadir Hct on severe AKI.

Various factors are involved in the incidence of postoperative AKI, including hemodynamic response, inflammation,
Table 1. Characteristics of patients stratified by nadir hematocrit quartiles.

| Variables                  | Total (n=1783) | Hematocrit (%) | P      |
|----------------------------|----------------|----------------|--------|
|                            |                | <25            | ≥25, and <28 | ≥28, and <31 | >31       |
| Age (years)                | 67.8±9.9       | 71.0±9.7       | 68.3±9.5   | 66.2±9.5     | 64.7±9.5  | <0.001  |
| Sex, n (%)                 |                |                |         |             |            | <0.001  |
| Female                     | 384 (21.5)     | 228 (42.1)     | 109 (27.3) | 10 (2.7)     | 7 (1.7)    |
| Male                       | 1399 (78.5)    | 314 (57.9)     | 291 (72.8) | 400 (90.9)   | 394 (98.3) |
| Race, n (%)                |                |                |         |             |            | 0.035   |
| White                      | 1249 (70.1)    | 361 (66.6)     | 272 (68)  | 317 (74.6)   | 299 (74.6) |
| Other                      | 534 (29.9)     | 181 (33.4)     | 128 (32)  | 40 (9.1)     | 7 (1.7)    |
| BMI (kg/m²)                | 30.2±5.5       | 28.6±5.3       | 29.7±5.6  | 30.7±5.1     | 32.2±5.4  | <0.001  |
| Comorbidities, n (%)       |                |                |         |             |            |         |
| Myocardial infarction      | 710 (39.8)     | 229 (42.3)     | 164 (41)  | 165 (37.5)   | 152 (37.9) | 0.366   |
| Congestive heart failure   | 367 (20.6)     | 135 (24.9)     | 90 (22.5) | 81 (18.4)    | 61 (15.2)  | 0.001   |
| Peripheral vascular disease| 202 (11.3)     | 83 (15.3)      | 43 (10.8) | 42 (9.5)     | 34 (8.5)   | 0.004   |
| Cerebrovascular disease    | 160 (9.0)      | 59 (10.9)      | 47 (11.8) | 34 (7.7)     | 20 (5)     | 0.002   |
| Chronic pulmonary disease  | 287 (16.1)     | 88 (16.2)      | 73 (18.2) | 71 (16.1)    | 55 (13.7)  | 0.382   |
| Rheumatic disease          | 51 (2.9)       | 20 (3.7)       | 20 (5)    | 6 (1.4)      | 5 (1.2)    | 0.002   |
| Diabetes without complication| 626 (35.1)   | 208 (38.4)     | 150 (37.5)| 146 (33.2)   | 122 (30.4) | 0.044   |
| Diabetes with complication | 173 (9.7)      | 48 (8.9)       | 51 (12.8) | 44 (10)      | 30 (7.5)   | 0.072   |
| Malignant cancer           | 37 (2.1)       | 11 (2)         | 14 (3.5)  | 8 (1.8)      | 4 (1)      | 0.092   |
| Vital signs                |                |                |         |             |            |         |
| Heart rate (beats/minute)  | 82.2±8.9       | 82.3±9.0       | 82.5±8.5 | 81.7±9.0     | 82.2±8.8  | 0.651   |
| Systolic BP (mm Hg)        | 111.0±6.8      | 110.6±7.0      | 111.5±6.9| 111.1±6.9    | 111.1±6.4 | 0.224   |
| Diastolic BP (mm Hg)       | 57.1±6.2       | 54.8±6.2       | 56.6±5.7 | 58.0±5.9     | 59.6±5.8  | <0.001  |
| Respiratory rate (breaths/min) | 18.2±2.5   | 17.9±2.5       | 18.1±2.5 | 18.3±2.5     | 18.5±2.4  | <0.001  |
| Temperature (°C)           | 37.2±0.4       | 37.2±0.4       | 37.2±0.4 | 37.3±0.4     | 37.3±0.4  | 0.020   |
| Laboratory results         |                |                |         |             |            |         |
| Glucose (mg/dL)            | 184.0 (164.0, 209.0) | 192.0 (171.0, 218.0) | 184.0 (164.0, 209.0) | 178.5 (161.0, 205.0) | 178.0 (158.0, 204.0) | <0.001 |
| SpO2 (%)                   | 92.9±4.3       | 93.0±5.2       | 93.4±2.6 | 92.5±5.0     | 92.5±3.1  | 0.012   |
| WBC (10⁹/L)                | 17.9±9.6       | 17.3±6.4       | 17.3±6.1 | 18.2±14.2    | 19.2±9.5  | 0.007   |
| Platelet (10⁹/L)           | 179.9±57.0     | 176.8±64.0     | 178.6±54.5| 179.5±55.7   | 185.9±50.1| 0.103   |
| Hemoglobin (g/dL)          | 11.5±1.5       | 10.4±1.3       | 11.0±1.2 | 11.9±1.1     | 12.9±1.1  | <0.001  |
and nephrotoxic factors [17]. One study attempting to predict AKI after cardiac surgery through a machine learning algorithm showed that preoperative hemoglobin, intraoperative urine output, and transfusion were the 3 most significant features in the model [3]. Anemia from hemodilution, a common method used to reduce blood viscosity and maintain baseline blood flow for oxygen delivery during CPB, is also one of the essential causes of low postoperative AKI [18]. To some extent, hemodilution could relieve renal ischemia while reducing the oxygen supply to cells. However, severe hemodilution can lead to kidney injury through decreased oxygen supply to the renal medulla and ischemia-reperfusion injury, especially in patients with atherosclerosis [19]. Hemodilution anemia is a modifiable risk factor that could be avoided through different kinds of management strategies during CPB, including conventional ultrafiltration [20]. Our analysis suggested that avoiding a certain degree of reduction in Hct might reduce the risk of severe AKI, but the effect was no longer apparent beyond a certain threshold. The use of allogeneic blood transfusion to increase Hct is controversial [21,22]. A prospective study suggested that a Hct value of 24% to 28% is safe for renal function during CPB, and a restrictive transfusion strategy may lead to improved clinical outcomes [23]. Although it was reported that low Hct is less harmful than increasing Hct by transfusion [15], some critically ill patients might benefit from preoperative transfusions [8]. For instance, a higher Hct level might outweigh the risk of transfusion in those who require prolonged mechanical ventilation after CABG [8]. Nevertheless, it is critical to avoid overperfusion in perioperative management and pay increased attention to homologous transfusion practices. An investigation inferred that an optimal preoperative Hct range of 42% to 46% helped to decreased morbidity.
and mortality [7]. Song et al [24] reported that erythropoietin treatment on the induction of anesthesia could decrease the rate of AKI. It is a promising approach in some patients with anemia to optimize preoperative Hct through injecting erythropoietin and iron [25,26]. Furthermore, a propensity score-matched study demonstrated that the utilization of ulinastatin could decrease the incidence of postoperative AKI after cardiac surgery with CPB; however, no significant differences were found in ICU stay and mortality compared with the control [17].

Although the baseline value of Hct was lower in female patients, a large single-center study including 13 734 patients demonstrated that lower nadir Hct during CPB was associated with a higher risk of AKI in male and female patients [27]. In accordance with the analysis by Brescia et al [1], we did not observe an interaction between sex and nadir Hct in patients who underwent OPCABG. In addition, we found an interaction between BMI and the effect of nadir Hct on severe AKI, which was more evident in patients without obesity. It is probable that patients without obesity tend to have lower Hct levels after OPCABG than patients with obesity. However, as approximately 7% of patients in the present study had missing weight values that were replaced by median values; therefore, this interaction might need further study to be confirmed.

This study also had some limitations. First, due to the retrospective observational nature of our analysis, we were unable to demonstrate the accuracy of the results. Second, although we adjusted for certain factors in the multivariate logistic regression model, some unknown confounding factors may have influenced our results. Third, this study analyzed only the association between the nadir Hct within 24 h after OPCAB and severe AKI, and did not analyze preoperative and intraoperative Hct data.

### Table 2. Relationship between nadir hematocrit and severe acute kidney injury in different models.

| Variable | Crude model | Model I | Model II |
|----------|-------------|---------|----------|
|          | OR (95% CIs)| OR (95% CIs) | OR (95% CIs) |
| Hct (%)  |            |         |          |
| <25      | 1 (Ref)    | 1 (Ref) | 1 (Ref)  |
| ≥5, and <28 | 0.23 (0.1-0.52)** | 0.24 (0.1-0.54)** | 0.33 (0.13-0.85)* |
| ≥28, and <31 | 0.18 (0.07-0.43)*** | 0.19 (0.08-0.46)*** | 0.18 (0.06-0.52)*** |
| ≥31      | 0.33 (0.16-0.67)** | 0.35 (0.16-0.76)** | 0.51 (0.19-1.36) |
| Trend.test | 0.59 (0.45-0.76)*** | 0.61 (0.46-0.89)*** | 0.68 (0.48-0.95)* |

Crude model: no covariates were adjusted. Model I adjusted for: age and g sex. Model II adjusted for: age, sex, race, BMI, myocardial infarction, congestive heart failure, peripheral vascular disease, rheumatic disease, diabetes with or without complication; systolic BP, diastolic BP, respiratory rate, temperature, glucose, SpO₂, WBC, platelets, anion gap, lactate, bicarbonate, chloride, sodium, potassium, APTT, SOFA, SAPSII, vasopressin, epinephrine, norepinephrine, and phenylephrine. Ref – reference; AKI – severe acute kidney injury; OR – odds ratio; CI – confidence interval; BMI – body mass index; BP – blood pressure; SpO₂ – pulse oxygen saturation; WBC – white blood cell; APTT – activated partial thromboplastin time; SOFA – sequential organ failure assessment; SAPSII – simplified acute physiology score II. * P<0.05; ** P<0.01; *** P<0.001.
Table 3. Subgroup analysis of the associations between hematocrit and severe acute kidney injury.

| Subgroup                  | n       | OR (95% CI) | P value | P for interaction |
|---------------------------|---------|-------------|---------|-------------------|
| **Age (y)**               |         |             |         |                   |
| <70                       | 1007.0  | 1 (0.87-1.15) | 0.981   | 0.305             |
| ≥70                       | 776.0   | 0.85 (0.74-0.97) | 0.017   |                   |
| **Sex, n (%)**            |         |             |         | 0.644             |
| Female                    | 384.0   | 0.15 (0.02-1.09) | 0.061   |                   |
| Male                      | 1399.0  | 0.95 (0.85-1.05) | 0.295   |                   |
| **Race, n (%)**           |         |             |         | 0.325             |
| White                     | 1249.0  | 0.96 (0.86-1.07) | 0.467   |                   |
| Other                     | 534.0   | 0.85 (0.72-1) | 0.056   |                   |
| **BMI (kg/m²)**           |         |             |         | 0.002             |
| <30                       | 982.0   | 0.77 (0.64-0.92) | 0.005   |                   |
| ≥30                       | 801.0   | 0.97 (0.86-1.1) | 0.611   |                   |
| **Myocardial infarction** |         |             |         | 0.908             |
| No                        | 1073.0  | 0.9 (0.79-1.03) | 0.131   |                   |
| Yes                       | 710.0   | 0.89 (0.78-1.02) | 0.097   |                   |
| **Congestive heart failure** |         |             |         | 0.672             |
| No                        | 1416.0  | 0.89 (0.78-1.01) | 0.075   |                   |
| Yes                       | 367.0   | 0.95 (0.83-1.09) | 0.49    |                   |
| **Systolic BP (mm Hg)**   |         |             |         | 0.808             |
| <110                      | 804.0   | 0.89 (0.8-1) | 0.056   |                   |
| ≥110                      | 979.0   | 0.95 (0.79-1.14) | 0.593   |                   |
| **Diastolic BP (mm Hg)**  |         |             |         | 0.124             |
| <60                       | 1212.0  | 0.87 (0.78-0.96) | 0.007   |                   |
| ≥60                       | 571.0   | 0.99 (0.74-1.32) | 0.945   |                   |
| **Anion gap (mmol/L)**    |         |             |         | 0.778             |
| <13                       | 797.0   | 0.89 (0.74-1.07) | 0.22    |                   |
| ≥13                       | 986.0   | 0.93 (0.83-1.04) | 0.187   |                   |
| **Sodium (mmol/L)**       |         |             |         | 0.196             |
| <138                      | 652.0   | 0.8 (0.61-1.05) | 0.114   |                   |
| ≥138                      | 1131.0  | 0.94 (0.85-1.04) | 0.204   |                   |
| **Lactate (mmol/L)**      |         |             |         | 0.982             |
| <2.6                      | 874.0   | 0.94 (0.79-1.12) | 0.491   |                   |
| ≥2.6                      | 909.0   | 0.93 (0.83-1.04) | 0.184   |                   |
Table 3 continued. Subgroup analysis of the associations between hematocrit and severe acute kidney injury.

| Subgroup        | n    | OR (95%CI)     | P value | P for interaction |
|-----------------|------|---------------|---------|-------------------|
| **Epinephrine use** |      |               |         |                   |
| No              | 1443.0 | 0.93 (0.82-1.06) | 0.304   |                   |
| Yes             | 340.0  | 0.88 (0.75-1.02) | 0.092   |                   |
| **Norepinephrine use** |      |               |         |                   |
| No              | 1503.0 | 0.9 (0.79-1.02)  | 0.098   |                   |
| Yes             | 280.0  | 1 (0.85-1.16)   | 0.949   |                   |
| **Phenylephrine use** |      |               |         |                   |
| No              | 713.0  | 0.95 (0.84-1.08) | 0.416   |                   |
| Yes             | 1070.0 | 0.9 (0.78-1.04)  | 0.141   |                   |
| **SAPSII** |      |               |         |                   |
| <36             | 899.0  | 1.05 (0.82-1.34) | 0.711   |                   |
| ≥36             | 884.0  | 0.89 (0.8-0.99)  | 0.029   |                   |

AKI – severe acute kidney injury; BMI – body mass index; BP – blood pressure; SAPSII – simplified acute physiology score II.

Conclusions

A nonlinear association was observed between postoperative nadir Hct and severe AKI in patients who underwent OPCABG. Lower nadir Hct was associated with an increased risk of severe AKI when the Hct value was less than 31%. However, no statistical significance was found in comparing the highest Hct group with the control group. Large prospective studies are required to further confirm our results.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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