Prognostic value of hematocrit levels among critically ill patients with acute kidney injury

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Abstract
The aim of this study was to investigate the value of hematocrit (HCT) level in predicting the outcomes of critically ill patients with acute kidney injury (AKI). A retrospective study of a total of 14,350 intensive care unit (ICU) patients, who were selected from Beth Israel Deaconess Medical Center (Boston, MA, USA) and met the inclusion criteria, was carried out. And the patient data were extracted from the Multiparameter Intelligent Monitoring in Intensive Care Database III version 1.3 (MIMIC-III v1.3). In our study, HCT quintiles were used to categorize the subjects into groups. The clinical outcomes were 30- and 90-day mortality in the ICU. Cox proportional-hazards models were used to evaluate the association between the HCT and survival. A total of 2827 30-day deaths and 3828 90-day deaths occurred. In univariate analysis, low HCT was significantly associated with increased 30- and 90-day mortality among females, which, however, was not observed in multivariate analysis adjusted for age, ethnicity, dialysate, continuous renal replacement therapy (CRRT), use of insulin, use of ventilator, AKI stages, and report of obesity. In subgroup analysis, an inverse association between HCT levels and risk of mortality for 90-day outcome was observed for female patients by exclusion of dialysate use, receiving CRRT, and obesity reports. Therefore, these findings suggest that lower HCT was associated with an increased risk of mortality in critically ill patients with AKI, and the effect appears to be stronger among women than men. The prognostic value of HCT seems dependent on other factors, for example, dialysate use, CRRT, and obesity. Further multicenter study is in demand to confirm the validity of the results presented in this article.

Keywords
acute kidney injury, hematocrit, intensive care unit

Date received: 10 December 2018; accepted: 4 April 2019

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Introduction

In the United States, there are more than 5 million patients admitted to intensive care units (ICUs) each year and many of them suffer acute kidney injury (AKI). Considering the high incidence of AKI among ICU patients and its poor prognosis, there have been accumulating studies over the past decades devoted to the identification of clinical predictors of mortality in AKI. Anemia develops rapidly in AKI and is usually mild and multi-factorial in origin. Numerous factors make contributions including hemodilution, hemolysis, bleeding, inhibition of erythropoiesis, and reduced red blood cell survival time. Therefore, hematocrit (HCT) level is strongly predictive of complications and death from cardiovascular causes in patients with kidney disease. Observational data indicate that the correction of anemia is associated with improved outcomes. HCT could indicate anemia in both individuals and populations. A HCT level of 33%–36% was suggested for anemia management in patients with kidney disease. However, whether HCT level itself causes or associates with mortality has yet to be determined given numerous factors affecting the outcome of AKI patients.

In this study, we aimed to clarify the association between HCT levels and prognosis in critically ill patients with AKI. For the endpoints of 30- and 90-day mortality, univariate and multivariate models were constructed based on gender-specific HCT quintiles. In multivariate models, covariates were adjusted for age, ethnicity (model I), as well as other confounding factors which are not fully studied (model II), for example, dialysate, continuous renal replacement therapy (CRRT), use of insulin and ventilator, AKI stages, and report of obesity. We conducted stratification analyses to examine whether the effect of HCT quintiles differed across various subgroups classified by these confounding factors.

Methods

Data source

This study was based on the publicly and freely available database known as the Multiparameter Intelligent Monitoring in Intensive Care Database III version 1.3 (MIMIC-III v1.3). The establishment of this database was approved by the institutional review boards of Massachusetts Institute of Technology (MIT; Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA). This database comprised de-identified health-related data associated with over 40,000 patients treated in a variety of critical care units at Beth Israel Deaconess Medical Center between 2001 and 2012.

Population selection criteria

Non-planned medical and surgical ICU admissions of ICU patients who satisfied the following inclusion criteria: age ≥ 18 years at the first admission and stayed in the hospital >2 days within the study period were initially analyzed. Patients were excluded from our study if more than 5% of their individual data were missing or there were outliers that exceeded the mean ± standard deviation (SD). Patients with malignant tumor were also excluded. The occurrence of AKI was determined based on the Kidney Disease: Improving Global Outcomes (KDIGO) classification.

Quintiles of HCT levels

Gender-specific quintiles of HCT levels were created and collapsed into four distinct categories for analysis according to a previous report. For women, ranges of HCT within the four groups were 9.00%–30.00% (low, Q1), 30.10%–34.50% (low to normal, Q2), 34.60%–39.50% (normal, Q3), and 39.60%–70.60% (high, Q4). For men, the ranges were 8.30%–29.20% (low, Q1), 29.30%–33.10% (low to normal, Q2), 33.20%–37.10% (normal, Q3), and 37.20%–75.00% (high, Q4). All analyses retained these gender-based pointcuts.

Statistical analysis

Baseline characteristics were grouped by HCT quintiles and expressed as frequencies (percentages) of categorical data and means ± SDs of continuous data. The primary endpoints were 30- and 90-day mortality. Comparisons between groups were made using the chi-square test for categorical variables and independent-samples t-test for continuous variables. Hazard ratio (HR) curves were created using the Kaplan–Meier method and differences among HCT categories were compared using the log-rank test. We used univariate and multivariable Cox proportional-hazards models to assess the association.
between baseline HCT and HR, with adjustment for the following potential confounders that have been previously associated with HCT and prognosis of ICU patients with AKI: age, ethnicity, AKI stages, and obesity. The results were presented as HRs with 95% confidence intervals (CIs). For the endpoint, two multivariate models were constructed based on the HCT group. In model I, covariates were adjusted only for age and ethnicity; in model II, we further adjusted for age, ethnicity, AKI stages, and obesity. We conducted stratification analyses to examine whether the effect of the HCT differed across various subgroups classified by ethnicity, AKI stages, and obesity. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 19.0. $P < 0.05$ was considered statistically significant.

### Results

**Association between HCT levels and 30- and 90-day outcome**

Our results showed that the cumulative hazard increased gradually as the HCT levels reduced from Q4 to Q1 in 90-day outcome, which were observed in both genders (Figure 1). In contrast, such trend was only found in females but not males in 30-day outcome (Figure 1).

As shown in Table 1, the log-rank $P$ value for the difference in 90-day outcome was determined as 0.024 and 2.047e–07 for males and females, respectively. As for the difference in 30-day outcome, statistical significance was observed in female patients ($P=0.017$), indicating the difference in response between the two genders.
Table 1. Log-rank analysis of 30- and 90-day prognosis among gender-specific quintiles of HCT levels.

|                | 30-day survival |         | 90-day survival |         |
|----------------|-----------------|---------|-----------------|---------|
|                | Chi-square      | P-value | Chi-square      | P-value |
| Male           | 2.819           | 0.420   | 9.42            | 0.024   |
| Female         | 10.159          | 0.017   | 33.93           | 2.047e–07 |

HCT: hematocrit.

Tables 2 and 3 show that there is an obvious difference between males and females. For males, compared with the univariate analysis, the multivariable-adjusted HRs of model I decreased at 30 days (Q2: 1.01–0.99, Q3: 1.01–0.97) and 90 days (Q2: 0.97–0.95, Q3: 0.92–0.89), except for the highest HCT category (Q4: 0.90–0.95 for 30 days and 0.82–0.86 for 90 days). On the contrary, the HRs of model II increased in all quintiles compared to the unadjusted model (30 days: 1.01–1.02 for Q2, 1.01–1.10 for Q3, and 0.90–1.09 for Q4; 90 days: 0.92–1.00 for Q3 and 0.82–0.98 for Q4). However, no statistical significance was observed for all the comparisons.

While, for females, the HRs of model I for 90-day outcome were 0.89 (95% confidence interval (CI): 0.79–1.00), 0.79 (95% CI: 0.70–0.89), and 0.79 (95% CI: 0.70–0.89), increasing HCT categories compared to the lowest HCT category as a reference, demonstrating an increased risk of mortality as the HCT decreased. The statistical analysis confirmed the significance of the comparisons (P < 0.05), indicating that HCT was associated with the mortality in critically ill AKI patients, regardless of age and ethnicity. However, no significance was observed in the comparison of the HRs of model I for the 30-day result.

It is worth noting that the HRs of model II for 90-day outcome were 0.94 (95% CI: 0.84–1.05), 0.90 (95% CI: 0.80–1.01), and 1.00 (95% CI: 0.88–1.13). The HCT categories had increased compared to the lowest HCT category as the reference. Similarly, the HRs of model II for 30-day outcome were 0.98 (95% CI: 0.85–1.12), 0.97 (95% CI: 0.84–1.12), and 1.15 (95% CI: 0.99–1.32) for the Q2, Q3, and Q4 categories. No significance was observed in the comparison of HRs of model II for both 30- and 90-day outcomes (P > 0.05).

Subgroup analyses

As for the use of dialysate, the HRs for female patients without report of dialysate use were 0.89

Table 2. Subgroup analysis of the associations between 30-day mortality and HCT for dialysate, CRRT, use of insulin and ventilators, AKI stages, and report of obesity.

|                | Female | Male |
|----------------|--------|------|
|                | Dialysate = No |     | Dialysate = Yes |
| Q1             | 1.0    | 1.0  |
| Q2             | 1.00 (0.85, 1.18) | 0.90 (0.77, 1.04) | 0.1497 |
| Q3             | 0.96 (0.81, 1.13) | 0.81 (0.70, 0.94) | 0.0071 |
| Q4             | 0.93 (0.79, 1.10) | 0.87 (0.75, 1.02) | 0.0810 |
|                | Insulin use = No |     | Insulin use = Yes |
| Q1             | 1.0    | 1.0  |
| Q2             | 0.97 (0.74, 1.27) | 0.87 (0.68, 1.10) | 0.2352 |
| Q3             | 1.00 (0.76, 1.30) | 0.65 (0.51, 0.84) | 0.0011 |
| Q4             | 0.87 (0.66, 1.14) | 0.65 (0.51, 0.85) | 0.0013 |
|                | CRRT = No |     | CRRT = Yes |
| Q1             | 1.0    | 1.0  |
| Q2             | 1.04 (0.85, 1.26) | 0.95 (0.80, 1.13) | 0.5638 |
| Q3             | 0.98 (0.81, 1.19) | 0.94 (0.80, 1.12) | 0.5054 |
| Q4             | 0.99 (0.81, 1.12) | 1.00 (0.86, 1.22) | 0.7749 |
|                | Ventilators use = No |     | Ventilators use = Yes |
| Q1             | 1.0    | 1.0  |
| Q2             | 0.89 (0.67, 1.19) | 0.83 (0.64, 1.07) | 0.1461 |
| Q3             | 0.93 (0.70, 1.24) | 0.78 (0.60, 1.01) | 0.0609 |
| Q4             | 0.77 (0.57, 1.04) | 0.68 (0.51, 0.90) | 0.0079 |
|                | AKI stage 1 |     | AKI stage 2 |
| Q1             | 1.0    | 1.0  |
| Q2             | 1.07 (0.77, 1.48) | 1.04 (0.74, 1.44) | 0.8361 |
| Q3             | 0.75 (0.53, 1.05) | 0.88 (0.63, 1.22) | 0.4289 |
| Q4             | 0.97 (0.70, 1.34) | 1.01 (0.73, 1.39) | 0.9605 |
|                | AKI stage 2 |     | AKI stage 2 |
| Q1             | 1.0    | 1.0  |
| Q2             | 0.98 (0.73, 1.31) | 0.86 (0.67, 1.11) | 0.2458 |
| Q3             | 1.15 (0.87, 1.53) | 0.79 (0.60, 1.02) | 0.0736 |
| Q4             | 0.89 (0.65, 1.22) | 0.90 (0.69, 1.17) | 0.4355 |
Table 2. (Continued)

| AKI stage | Male | Female |
|-----------|------|--------|
| Q1 1.0 | 1.0 |
| Q2 1.03 (0.82, 1.29) 0.8092 | 0.99 (0.82, 1.19) 0.9118 |
| Q3 1.16 (0.92, 1.45) 0.2155 | 1.06 (0.88, 1.29) 0.5247 |
| Q4 1.14 (0.90, 1.44) 0.2686 | 1.27 (1.04, 1.55) 0.0216 |
| Obesity = No | | |
| Q1 1.0 | 1.0 |
| Q2 0.99 (0.84, 1.16) 0.8580 | 0.91 (0.79, 1.04) 0.1691 |
| Q3 0.99 (0.85, 1.16) 0.9419 | 0.84 (0.73, 0.97) 0.0184 |
| Q4 0.95 (0.81, 1.12) 0.5220 | 0.89 (0.77, 1.02) 0.0965 |
| Obesity = Yes | | |
| Q1 1.0 | 1.0 |
| Q2 1.79 (0.73, 4.41) 0.2037 | 2.88 (0.76, 10.87) 0.0191 |
| Q3 0.95 (0.81, 1.12) 0.5220 | 0.89 (0.77, 1.02) 0.0965 |

HCT: hematocrit; CRRT: continuous renal replacement therapy; AKI: acute kidney injury.

Table 3. Subgroup analysis of the associations between 90-day mortality and HCT for dialysate, CRRT, use of insulin and ventilators, AKI stages, and report of obesity.

| AKI stage | Male | Female |
|-----------|------|--------|
| Q1 1.0 | 1.0 |
| Q2 1.03 (0.82, 1.29) 0.8092 | 0.99 (0.82, 1.19) 0.9118 |
| Q3 1.16 (0.92, 1.45) 0.2155 | 1.06 (0.88, 1.29) 0.5247 |
| Q4 1.14 (0.90, 1.44) 0.2686 | 1.27 (1.04, 1.55) 0.0216 |
| Q1 1.0 | 1.0 |
| Q2 0.94 (0.82, 1.09) 0.4199 | 0.95 (0.78, 1.01) 0.0642 |
| Q3 0.89 (0.77, 1.03) 0.1130 | 0.78 (0.69, 0.89) 0.0002 |
| Q4 0.85 (0.73, 0.98) 0.0270 | 0.80 (0.70, 0.92) 0.0012 |
| Q1 1.0 | 1.0 |
| Q2 0.99 (0.84, 1.17) 0.9402 | 0.95 (0.81, 1.06) 0.0214 |
| Q3 0.89 (0.71, 1.12) 0.3322 | 0.85 (0.73, 0.98) 0.0010 |
| Q4 0.78 (0.61, 0.99) 0.0388 | 0.85 (0.73, 0.98) 0.0002 |

Dialysate = No

| Q1 1.0 | 1.0 |
| Q2 0.96 (0.73, 1.24) 0.2957 | 0.91 (0.77, 1.06) 0.0227 |
| Q3 0.75 (0.60, 0.95) 0.0166 | 0.71 (0.57, 0.87) 0.0011 |
| Q4 0.65 (0.51, 0.83) 0.0005 | 0.61 (0.49, 0.77) <0.0001 |

Dialysate = Yes

| Q1 1.0 | 1.0 |
| Q2 1.06 (0.90, 1.25) 0.3524 | 1.07 (0.90, 1.25) 0.0001 |
| Q3 0.95 (0.78, 1.19) 0.0108 | 0.87 (0.70, 1.03) 0.1214 |
| Q4 0.92 (0.71, 1.20) 0.0592 | 0.82 (0.65, 1.03) 0.0875 |

(Continued)
In relation to obesity, the HRs of female subjects without obesity reports were 0.88 (95% CI: 0.79–0.99), 0.79 (95% CI: 0.70–0.89), and 0.79 (95% CI: 0.70–0.90), respectively, to increase the HCT categories. In comparison, such trend was not observed for the counterparts who have reports of obesity, such as 1.95 (95% CI: 0.65–5.84), 1.36 (95% CI: 0.44–4.15), and 1.56 (95% CI: 0.53–4.57) for increasing HCT categories.

**Table 3.** (Continued)

| AKI Stage 3 | Male | Female |
|-------------|------|--------|
| Q1          | 1.0  | 1.0    |
| Q2          | 1.01 (0.83, 1.22) 0.9226 | 0.96 (0.82, 1.13) 0.6277 |
| Q3          | 1.02 (0.83, 1.24) 0.8671 | 1.03 (0.88, 1.22) 0.6938 |
| Q4          | 1.00 (0.81, 1.23) 0.9938 | 1.10 (0.92, 1.32) 0.2977 |

| Obesity | Male | Female |
|---------|------|--------|
| No      | Q1   | 1.0    |
|         | Q2   | 0.95 (0.83, 1.08) 0.4265 | 0.88 (0.79, 0.99) 0.0358 |
|         | Q3   | 0.91 (0.79, 1.04) 0.1627 | 0.79 (0.70, 0.89) 0.0001 |
|         | Q4   | 0.85 (0.74, 0.98) 0.0283 | 0.79 (0.70, 0.90) 0.0002 |
| Yes     | Q1   | 1.0    |
|         | Q2   | 1.60 (0.70, 3.67) 0.2678 | 1.95 (0.65, 5.84) 0.2306 |
|         | Q3   | 0.47 (0.15, 1.49) 0.1967 | 1.36 (0.44, 4.15) 0.5934 |
|         | Q4   | 0.79 (0.30, 2.03) 0.6199 | 1.56 (0.53, 4.57) 0.4190 |

HCT: hematocrit; CRRT: continuous renal replacement therapy; AKI: acute kidney injury.

In relation to obesity, the HRs of female subjects without obesity reports were 0.88 (95% CI: 0.79–0.99), 0.79 (95% CI: 0.70–0.89), and 0.79 (95% CI: 0.70–0.90), respectively, to increase the HCT categories. In comparison, such trend was not observed for the counterparts who have reports of obesity, such as 1.95 (95% CI: 0.65–5.84), 1.36 (95% CI: 0.44–4.15), and 1.56 (95% CI: 0.53–4.57) for increasing HCT categories.

**Discussion**

In this study, we examined HCT level as a potential prognostic, non-specific risk factor for 30- and 90-day mortality of ICU-admitted patients with AKI. We found that the risk of mortality for 90-day outcome was inversely associated with HCT levels in both genders. Notably, a similar finding reported by Ellis et al. showed that lower HCT was associated with an increased risk of AKI. However, the effect appears to be stronger among men than women, which is different from our results.

Univariate and multivariate Cox proportional-hazards regression analyses showed that HCT was associated with HRs for 90-day mortality independent of age and ethnicity in females. However, no statistical significance was observed in model II with covariates adjusted for additional characteristics, including dialysate, CRRT, insulin and ventilator use, AKI stages, and obesity, suggesting the dependency of HCT for prognosis on these factors. Consistently, according to previous reports, some factors have been shown to be closely involved in the intervention and management of AKI patients. In the subgroup analysis, an inverse association between HCT levels and risk of mortality for the 90-day outcome was observed for female patients by exclusion of dialysate use. Similar results were also found in the cases without CRRT and obesity reports. These findings were consistent with previous reports. For example, CRRT and dialysis interventions are widely used for the treatment of AKI as a standard and able to result in improved outcomes. Besides, Danziger et al. revealed that obesity was a risk factor for AKI injury associated with increased mortality. In contrast, there is no difference in the changes of HRs for 90-day outcome between the cases that female patients use ventilator or not. The association between obesity and AKI has been reported and insulin resistance is recognized as one of the hallmark systemic abnormalities. In our results, no difference was observed between the cases that female patients use insulin or not.

In our results, an inverse association was found in females with moderate AKI (stages 1 and 2) which was confirmed with statistical significance ($P < 0.05$). In contrast, opposite results were found for females with severe AKI (stage 3) without statistical significance. A similar trend was also seen in male patients.

There are several types of ICU patients, such as those with dengue fever. Ranjit et al. showed that the patients who had died of dengue were significantly positively associated with low HCT level before ICU discharge.

In conclusion, these findings suggest that lower HCT is associated with an increased risk of mortality in critically ill patients with AKI, and the effect appears to be stronger among women than men. The prognostic value of HCT seems dependent on other factors, which demands further studies to confirm the validity of the results.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of
this article: This research was supported by grants from the Wenzhou Committee of Science and Technology of China (Y20170055 and ZS2017008).

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