Plasma Catalytic Iron, AKI, and Death among Critically Ill Patients

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Abstract

Background and objectives Catalytic iron has been hypothesized to be a key mediator of AKI. However, the association between plasma catalytic iron levels and AKI has not been well studied in humans.

Design, settings, participants, & measurements A single-center, prospective, nonconsecutive cohort study of 121 critically ill patients admitted to intensive care units (ICUs) between 2008 and 2012 was performed. Plasma catalytic iron, free hemoglobin, and other iron markers were measured on ICU days 1 and 4. The primary end point was in-hospital mortality or AKI requiring RRT. Secondary end points included mortality (assessed during hospitalization, at 30 days, and 1 year) and incident AKI, defined by modified Kidney Disease Improving Global Outcomes criteria.

Results ICU day 1 plasma catalytic iron levels were higher among patients who reached the primary end point (median, 0.74 μmol/l [interquartile range, 0.31–3.65] versus 0.29 μmol/l [0.22–0.46]; $P<0.01$). ICU day 1 plasma catalytic iron levels were associated with number of packed red blood cell transfusions before ICU arrival ($r_s=0.29$; $P<0.001$) and plasma free hemoglobin levels on ICU day 1 ($r_s=0.32$; $P<0.001$). Plasma catalytic iron levels on ICU day 1 were significantly associated with in-hospital mortality or AKI requiring RRT, even after adjusting for age, enrollment eGFR, and number of packed red blood cell transfusions before ICU arrival (13 events; adjusted odds ratio per 1-SD higher ln[catalytic iron], 3.33; 95% confidence interval, 1.79 to 6.20). ICU day 1 plasma catalytic iron levels were also significantly associated with incident AKI, RRT, hospital mortality, and 30-day mortality.

Conclusions Among critically ill patients, elevated plasma catalytic iron levels on arrival to the ICU are associated with a greater risk of incident AKI, RRT, and hospital mortality.

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Introduction

Animal models suggest that catalytic iron has a pathologic role in AKI (1). Catalytic iron is defined as the component of circulating iron that is neither transferrin nor protein bound and is therefore capable of catalyzing the Fenton and Haber–Weiss reactions, generating hydroxyl radicals, and causing cellular oxidative damage (2,3).

In animal models, catalytic iron has been implicated in nephrotoxicity resulting from ischemia-reperfusion (4), aminoglycosides (5), cisplatin (6), rhabdomyolysis (7), and hemoglobinuria (8). In many of these models, treatment with an iron chelator is protective (5,6,9,10). In humans, the release of intracellular stores of iron under conditions of tissue injury (3) or hemolysis (11) results in elevated circulating levels of catalytic iron. High plasma catalytic iron levels, in turn, may have a pathologic role in a variety of disease states, including coronary artery disease (12,13) and acute coronary syndrome (14–16); however, the association with AKI has not been well studied in humans.

We studied patients with critical illness because of the high AKI event rate (17) and the considerably increased morbidity and mortality associated with AKI in this setting (18). In addition, critically ill patients have high rates of hemolysis, tissue injury, and transfusion of packed red blood cells (pRBCs), all of which may contribute to elevated plasma catalytic iron levels. We hypothesized that elevated plasma catalytic iron levels are associated with an increased risk of in-hospital mortality or AKI requiring RRT (death/RRT) among critically ill patients.

Materials and Methods

Study Design

We conducted a prospective cohort study among patients admitted to intensive care units (ICUs) at Brigham and Women's Hospital (Boston, MA) between October 2008 and November 2012. Patients or their surrogates provided written informed consent and all protocols were approved by the Partners Human Research Committee (the Brigham and Women's Hospital Institutional Review Board).

Enrollment Criteria

Inclusion criteria were age >18 years and admission to a medical or surgical ICU. Exclusion criteria were as

follows: (*1*) anticipated ICU stay <24 hours, (*2*) admitted to the ICU for a low-risk condition such as airway monitoring or serial neurologic checks, (*3*) serum creatinine (SCr) >4.5 mg/dl or receiving dialysis, (*4*) pregnancy, and (*5*) enrollment in a conflicting research study.

Study Procedures

ICU patients were screened and enrolled intermittently throughout the study period, without relation to the time of year, patient characteristics, or physician characteristics. We collected plasma samples at two time points: within 24 hours of ICU arrival and 72 hours later (hereafter referred to as ICU days 1 and 4, respectively). We stored plasma aliquots at −80°C within 2 hours of collection.

Clinical Outcomes

Investigator D.E.L. adjudicated all outcomes by reviewing discharge summaries and progress notes, and was blinded to all study measurements at the time of adjudication. The prespecified primary end point was the composite of death/RRT. Secondary end points were RRT, mortality (assessed during hospitalization and at 30-days and 1-year), and AKI. To maintain the prospective nature of the study, we evaluated incident AKI (occurring after enrollment/arrival to the ICU). AKI was defined and staged according to the SCr-based criteria established by the Kidney Disease Improving Global Outcomes Work Group (19). Urine output data were not available. AKI was defined as an absolute ≥0.3 mg/dl increase in SCr over any 48-hour time period during hospitalization, or an increase in SCr≥1.5 times baseline within 7 days. AKI stage was defined as follows: stage 1, increase in SCr 1.5–1.9 times baseline or absolute increase ≥0.3 mg/dl; stage 2, increase in SCr 2.0–2.9 times baseline; and stage 3, increase in SCr≥3.0 times baseline, or increase in SCr to ≥4.0 mg/dl, or initiation of RRT.

Additional end points included the duration of mechanical ventilation and the hospital length of stay. To avoid the confounding effect of mortality, we calculated ventilator-free days and hospital-free days, defined as 28 minus the number of ventilator-dependent days or hospitalization days, respectively, assuming survival to 28 days or discharge from the hospital. Patients who died before 28 days were assigned a score of zero (20).

Laboratory Analyses

SCr was measured for clinical purposes using a modified kinetic Jaffe method. Plasma catalytic iron and other iron markers were measured in samples taken from ICU days 1 and 4. These samples were sent at −70°C to the Muljibhai Patel Society for Research in Nephro-Urology (Nadiad, India), using a validated thermal packing kit (Minnesota Thermal Science, Plymouth, MN). Catalytic iron levels were measured using the modified bleomycin assay (14). In brief, the antitumor agent, bleomycin, reacts with and degrades DNA in the presence of catalytic iron and a suitable reducing agent. The DNA degradation products react with thiobarbituric acid to form a chromogen, the intensity of which is measured at 532 nm using a Beckman (DU800) spectrophotometer. The assay measures only free iron content in the sample, which is capable of taking part in the generation of reactive oxygen species. The assay is not affected by the presence of free hemoglobin, transferrin, catalase, or lactoferrin in the sample.

In addition to catalytic iron, we also measured plasma total iron, transferrin, ferritin, and free hemoglobin (additional details are provided in the Supplemental Methods). Total iron binding capacity (TIBC) was estimated from the transferrin concentration. The percentage of transferrin saturation was calculated as the ratio of total iron (in micrograms per deciliter)/TIBC (in micrograms per deciliter), multiplied by 100. Total imprecision was calculated for each of the assays using blinded split samples. Interassay coefficients of variation for catalytic iron, total iron, transferrin, TIBC, and ferritin were 5.4%, 1.3%, 1.4%, 3.8%, and 9.4%, respectively.

Statistical Analyses

Statistical analysis was performed with SAS software (version 9.3; SAS Institute Inc, Cary, NC). Data are reported as median and interquartile range (IQR; 25th–75th percentiles). Comparison of iron markers over time (ICU day 1 versus day 4) was assessed using the Wilcoxon signed-rank test. Comparison of iron markers between patients who reached the composite end point (death/RRT) versus those who did not was assessed using the Wilcoxon rank-sum test. Correlations between catalytic iron with free hemoglobin, number of pRBC transfusions, and AKI stage were analyzed using Spearman's rank correlation coefficient. Differences in catalytic iron levels on ICU day 1 based on differences in the cause of AKI were assessed using the Kruskal–Wallis test.

Univariate logistic regression was used to assess the relation between iron markers (both ICU days 1 and 4) with death/RRT. Multivariable logistic regression models were used to compute adjusted odds ratios for catalytic iron levels (ICU day 1) and death/RRT and secondary end points. The models were adjusted for age, enrollment eGFR, and number of pRBC transfusions within 48 hours before ICU arrival. We also analyzed catalytic iron levels by tertiles and used the Cochran–Armitage test for trend to assess the association between catalytic iron levels (ICU day 1) and death/RRT as well as the association with AKI. All comparisons are two-tailed, with $P<0.05$ considered significant.

Results

Baseline Characteristics

We enrolled and collected samples from 121 patients. The median age was 62 years (IQR, 56–73). The most common comorbidities were hypertension (53%), chronic lung disease (31%), and malignancy (28%). The majority of patients (84%) were admitted to a surgical ICU. Additional baseline characteristics are shown in Table 1.

Plasma Iron Markers on ICU Days 1 and 4

Plasma iron markers from ICU days 1 and 4 are shown in Table 2. Compared with standard reference ranges from healthy participants, plasma free hemoglobin and ferritin levels were on the high end of the normal range and transferrin levels were low. We did not detect any significant changes in iron markers over time.

Plasma iron markers from patients who survived without RRT (n=108) versus those who experienced death/RRT (n=13) are shown in Figure 1. Patients who reached the composite end point of death/RRT had higher catalytic

Table 1. Baseline characteristics (*N*=121 patients)

Characteristic	Value
Demographic	
Age (yr)	62 (56–73)
Women	46 (38)
White	112 (93)
Renal function on enrollment	
Serum creatinine (mg/dl)	0.8 (0.7–1.0)
eGFR (ml/min per 1.73m^2)	89 (73–99)
Comorbidity	
Hypertension	64 (53)
Chronic lung disease	37 (31)
Active malignancy	34 (28)
Diabetes mellitus	29 (24)
CKD	7 (6)
Congestive heart failure	4 (3)
Chronic liver disease	3 (2)
ICU type	
Surgical	102 (84)
SICU	66 (54)
TICU	36 (30)
Nonsurgical	19 (16)
CCU	11 (9)
MICU	8 (7)
Other	
Status of procedure (for surgical patients)	
Elective	41 (34)
Urgent	57 (47)
Days in hospital before enrollment (*n*)	1 (1–3)

Data are presented as the median and interquartile range (25th–75th percentiles) for continuous variables and *n* (%) for binary variables. eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation. The SICU cares for general surgical patients as well as trauma/burn patients. The TICU cares for patients requiring noncardiac thoracic/pulmonary surgery. ICU, intensive care unit; SICU, surgical/trauma ICU; TICU, thoracic ICU; CCU, cardiac care unit; MICU, medical ICU.

iron levels on ICU days 1 and 4 and higher ferritin levels on ICU day 1 compared with those who did not.

Factors Associated with Plasma Catalytic Iron Levels

Baseline/ICU Characteristics. Plasma catalytic iron levels on ICU day 1 did not differ by age, sex, comorbidities, type of ICU (surgical versus nonsurgical), or status of procedure (urgent versus elective). Furthermore, we found no correlation between catalytic iron levels and eGFR (Supplemental Figure 1), suggesting that decreased filtration does not significantly affect plasma levels.

pRBC Transfusions. Because pRBCs undergo hemolysis over time (21–23), resulting in the release of free hemoglobin, we investigated the association between pRBC transfusions within 48 hours before ICU arrival and levels of plasma catalytic iron and free hemoglobin on ICU day 1. We found a significant association between the number of pRBC transfusions and catalytic iron levels, as well as a significant (albeit weaker) association with free hemoglobin levels (Figure 2).

Free Hemoglobin. Because free hemoglobin resulting from hemolysis or pRBC transfusions could be a source of catalytic iron, we investigated the association between plasma free hemoglobin and catalytic iron levels. We found significant associations between plasma free hemoglobin and plasma catalytic iron levels on both ICU day 1 (r_s=0.32; P<0.001) and day 4 (r_s=0.39; P<0.001) (Supplemental Figure 2).

Cause of AKI. The most common causes of AKI (diagnosed on a clinical basis and not biopsy proven) were ischemic acute tubular necrosis (21.2%), sepsis (21.2%), and prerenal azotemia (15.2%). Additional data on the cause of AKI are shown in Supplemental Table 1. No statistically significant differences in ICU day 1 plasma catalytic iron levels were observed between patients with different causes of AKI (Supplemental Figure 3).

Catalytic Iron and Adverse Outcomes

Among the 121 patients, 13 reached the composite end point of death/RRT (eight died without RRT, four required RRT and survived, and one required RRT and died). Among the 13 patients who reached the composite end point of death/RRT, 12 (92.3%) were admitted to a surgical ICU and one (7.7%) was admitted to a medical ICU. Incident AKI after ICU arrival occurred in 33 patients (an additional 11 had established AKI on arrival to the ICU). Among the 33 patients with incident AKI, 28 (84.8%) were admitted to a surgical ICU and five (15.2%) were admitted to a medical ICU.

In univariate analyses, catalytic iron and ferritin levels measured on ICU day 1 were significantly associated with death/RRT, whereas other iron markers and baseline characteristics were not (Table 3). Because the strongest

Table 2. Plasma iron markers on ICU days 1 and 4

Iron Marker	Reference Range	ICU Day 1 (*n*=119)	ICU Day 4 (*n*=104)	*P* Value
Catalytic iron (μmol/l)	Undefined	0.3 (0.2–0.5)	0.3 (0.3–0.5)	0.71
Free hemoglobin (mg/dl)	0–15	14 (8–25)	12 (7–23)	0.56
Total iron (μg/dl)	50–150 (men); 35–145 (women)	86 (69–98)	87 (73–97)	0.47
Transferrin (mg/dl)	200–360	139 (88–191)	136 (89–190)	0.40
Transferrin saturation (%)	14–50	43 (34–55)	43 (34–58)	0.42
Ferritin (ng/ml)	24–336 (men); 11–307 (women)	324 (153–676)	324 (162–544)	0.48

Data are presented as median and interquartile range (25th–75th percentiles).

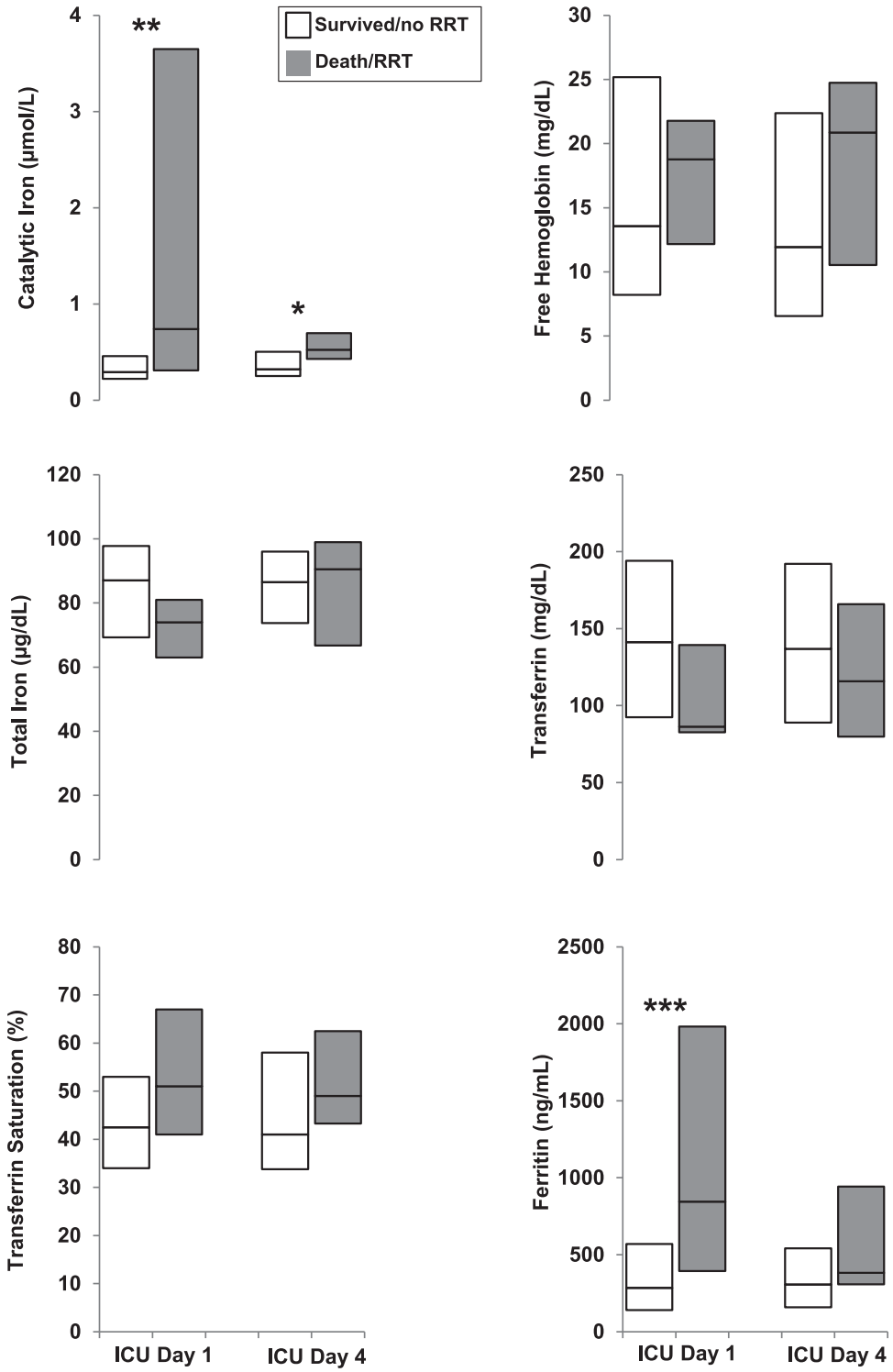

Figure 1. | **Plasma iron markers: survival without RRT (*n*=108) versus death/RRT (*n*=13).** *$P<0.05$; **$P<0.01$; and ***$P<0.001$ for between-group comparisons. Bars represent median and (interquartile range) (25th–75th percentiles). Death/RRT, hospital mortality or AKI requring RRT; ICU, intensive care unit.

univariate associations were observed on ICU day 1, subsequent analyses focused on this time point.

Table 4 shows the unadjusted and adjusted associations between catalytic iron levels on ICU day 1 and the primary and secondary end points. Plasma catalytic iron levels on ICU day 1 were significantly associated with death/RRT, even after adjusting for age, enrollment eGFR, and number of pRBC transfusions within 48 hours before ICU arrival (adjusted odds ratio per 1-SD higher ln[catalytic iron], 3.33; 95% confidence interval, 1.79 to 6.20). In addition,

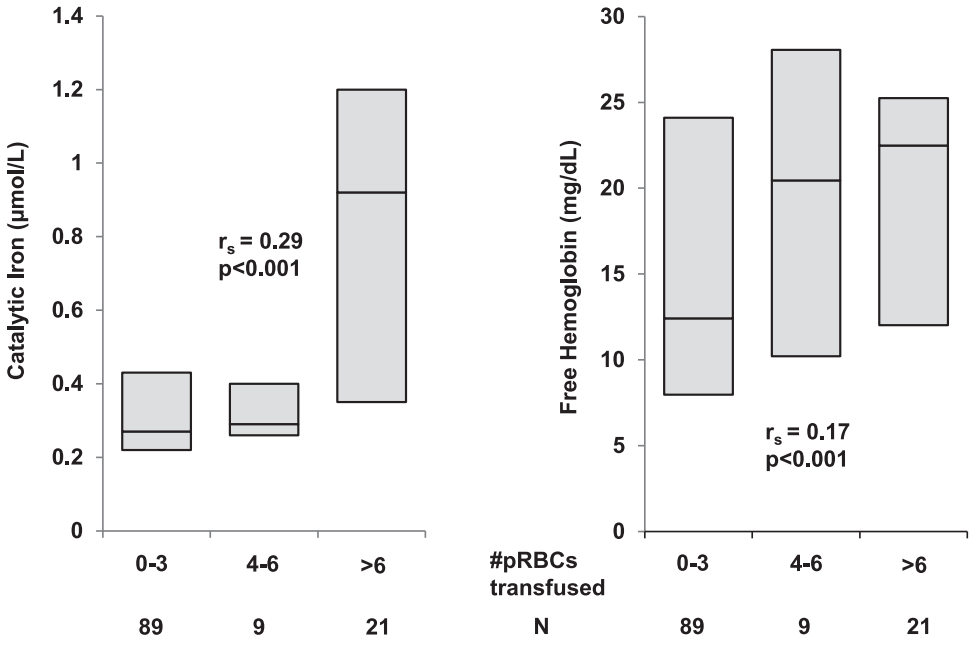

Figure 2. | **Plasma catalytic iron and free hemoglobin levels on ICU day 1 by number of pRBCs transfused.** Only pRBCs administered within 48 hours before ICU arrival were included. Bars represent median and interquartile range (25th–75th percentiles). pRBC, packed red blood cell.

Table 3. Univariate associations between plasma iron markers and baseline characteristics with death/RRT

Time Point	OR (95% CI)	*P* Value
Catalytic iron		
ICU day 1	2.90 (1.67 to 5.02)	<0.001
ICU day 4	1.94 (1.00 to 3.73)	0.05
Free hemoglobin		
ICU day 1	1.24 (0.67 to 2.30)	0.50
ICU day 4	1.62 (0.70 to 3.71)	0.26
Total iron		
ICU day 1	0.81 (0.48 to 1.39)	0.45
ICU day 4	1.02 (0.49 to 2.12)	0.96
Transferrin		
ICU day 1	0.67 (0.37 to 1.20)	0.18
ICU day 4	0.79 (0.38 to 1.61)	0.51
Transferrin saturation		
ICU day 1	1.58 (0.86 to 2.88)	0.14
ICU day 4	1.46 (0.71 to 3.00)	0.30
Ferritin		
ICU day 1	3.22 (1.59 to 6.52)	0.001
ICU day 4	1.92 (0.88 to 4.17)	0.10
Baseline characteristic		
Age (per 10 yr)	1.19 (0.77 to 1.84)	0.43
eGFR (per 10 ml/min per 1.73m^2)	0.97 (0.78 to 1.22)	0.80
Urgent procedure	2.73 (0.54 to 13.88)	0.23

All iron markers are natural log-transformed, given their skewed distribution, and standardized to 1 SD to allow comparison across biomarkers. OR, odds ratio; 95% CI, 95% confidence interval.

catalytic iron levels were associated with RRT, hospital mortality, 30-day mortality, and incident AKI in unadjusted analyses. After adjustment for age, enrollment eGFR, and number of pRBC transfusions within 48 hours before ICU arrival, these associations were strengthened. Figure 3 shows the dose-response relation between tertiles of catalytic iron levels on ICU day 1 and death/RRT and incident AKI. Figure 4 shows the dose-response relation between higher catalytic iron levels on ICU day 1 and greater severity of AKI.

Finally, a significant inverse correlation was observed between catalytic iron levels on ICU day 1 and hospital-free days (r_s=−0.33; P<0.001), implying longer duration of hospitalization among participants with higher catalytic iron levels. This association was not observed for ventilator-free days (r_s=−0.05; P=0.68).

Discussion

In this prospective cohort study, we report that higher plasma catalytic iron levels on arrival to the ICU are associated with an increased risk of death/RRT as well as hospital and 30-day mortality, AKI incidence and severity, and longer hospital stay. Moreover, these associations persisted after adjusting for potential confounders including pRBC transfusions, which are likely to be a source of catalytic iron as well as an indicator of severity of illness. These findings support the notion that catalytic iron plays an important role in mediating AKI and death among critically ill patients.

Our findings are consistent with and expand on prior studies of iron and AKI. Iron has long been hypothesized to serve as a potential mediator of oxidative stress and cellular injury. By catalyzing the Haber–Weiss and Fenton reactions, catalytic iron combines with superoxide to ultimately form the very reactive and injurious hydroxyl radical (2,24). In the kidney, iron impairs proliferation of renal tubular epithelial cells *via* dysregulation of cell-matrix adhesion (25). In animal models of AKI, catalytic iron levels are elevated in the

Table 4. Association between plasma catalytic iron levels on ICU day 1 and adverse outcomes

Outcome	Events (*n*)	Unadjusted		Adjusted	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Primary end point					
Death/RRT	13	2.90 (1.67 to 5.02)	<0.001	3.33 (1.79 to 6.20)	<0.001
Secondary end points					
RRT	5	3.43 (1.54 to 7.63)	0.003	3.93 (1.48 to 10.44)	0.01
Hospital mortality	9	2.47 (1.38 to 4.43)	0.002	2.93 (1.52 to 5.63)	0.001
30-d mortality	13	1.65 (1.01 to 2.72)	0.05	1.90 (1.10 to 3.28)	0.02
1-yr mortality	36	1.40 (0.96 to 2.05)	0.09	1.38 (0.91 to 2.10)	0.13
Incident AKI	33	1.61 (1.08 to 2.39)	0.02	1.67 (1.04 to 2.67)	0.03

Catalytic iron levels are natural log-transformed, given their skewed distribution, and standardized to 1 SD. Adjusted models include age, enrollment eGFR, and number of packed red blood cell transfusions within 48 hours before ICU arrival. Death/RRT, hospital mortality or AKI requiring RRT.

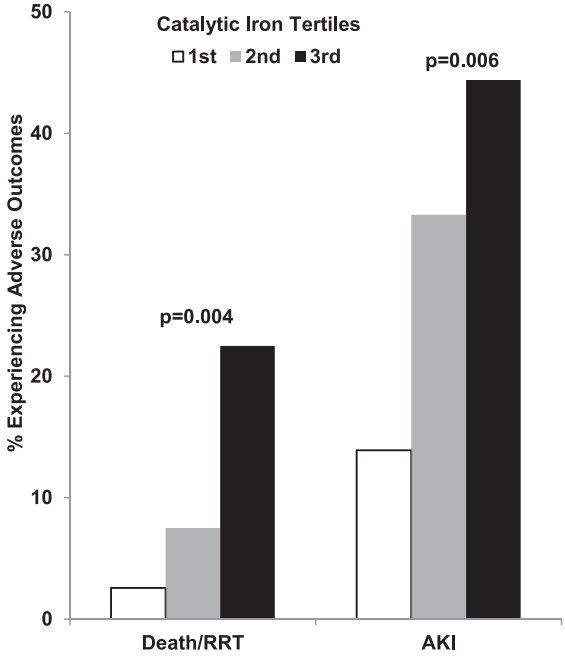

Figure 3. | Death/RRT and incident AKI by tertiles of catalytic iron on ICU day 1.

kidneys after a wide range of insults, including ischemia-reperfusion (4), aminoglycosides (5), cisplatin (6), rhabdomyolysis (7), and hemoglobinuria (8). In many of these models, treatment with an iron chelator is protective (5,6,9,10).

An important role of iron in mediating AKI is also suggested by studies in humans. Elevated levels of urinary hepcidin, a peptide hormone that decreases iron efflux out of cells and into the circulation, are associated with protection against AKI after cardiac surgery (26,27). In addition, one study randomized 30 critically ill patients with hypotension to receive deferoxamine and *N*-acetylcysteine versus placebo (28). The authors reported lower SCr levels at hospital discharge in the active treatment group (28). A larger follow-up study (*n*=140) is underway (ClinicalTrials.gov identifier NCT00870883).

Despite compelling data from animal studies and indirect evidence in humans, few studies have directly assessed the association between catalytic iron and AKI in humans. In a pilot study of 14 patients undergoing cardiac surgery, urinary catalytic iron levels increased significantly within 8 hours in patients who developed AKI (29). In a larger study (*n*=806), plasma catalytic iron levels measured 24 hours after radiocontrast administration were higher among patients with versus without established contrast nephropathy (15). To our knowledge, no other study has documented elevated plasma catalytic iron levels in humans with AKI. Moreover, no study has prospectively reported on elevated plasma catalytic iron levels and incident AKI.

In addition to documenting an association between catalytic iron and AKI, we also found a significant association between catalytic iron and hospital and 30-day mortality. Although AKI is a well known risk factor for increased hospital mortality (30), five of the nine patients who died in the hospital did not have AKI, raising the possibility that catalytic iron may be toxic to multiple organ systems and not just the kidneys. Consistent with this possibility, elevated plasma catalytic iron levels are associated with increased mortality in other settings, including patients with acute coronary syndrome (15,16).

Although this study could not determine the source(s) of catalytic iron, we found a significant association between plasma catalytic iron and free hemoglobin levels, suggesting that free hemoglobin from *ex vivo* hemolysis (*e.g.*, pRBC transfusions) and/or *in vivo* hemolysis (*e.g.*, sepsis) (31,32) are potentially relevant sources. Supporting this notion, we found a significant dose-response relation between pRBC transfusions before ICU arrival and plasma catalytic iron levels on ICU day 1. An additional potential source of catalytic iron in critically ill patients is tissue injury resulting from ischemia and inflammation (33,34). The importance of inflammation in mediating AKI is highlighted by the finding that ferritin levels on ICU day 1 were associated with death/RRT. In this setting, ferritin is likely to be elevated as an acute phase reactant, identifying patients with greater severity of illness.

We acknowledge several limitations of this study, including observational design, modest sample size, and enrollment

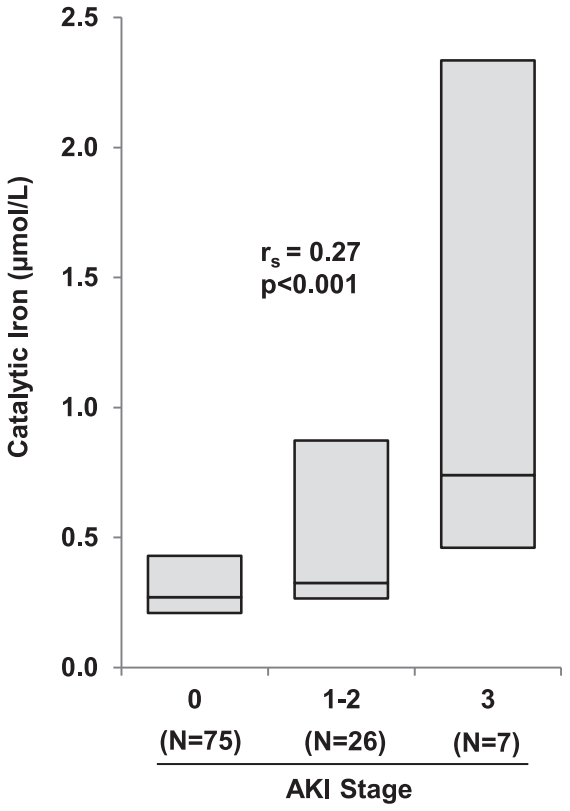

Figure 4. | Catalytic iron levels on ICU day 1 by AKI severity. Bars represent median and interquartile range (25th–75th percentiles).

of patients predominantly from surgical ICUs. By virtue of the single-center study design, the results may not be generalizable to other medical or surgical ICU settings. We did not measure all potentially relevant iron markers such as haptoglobin, hemopexin, and other proteins involved in iron transport and regulation such as hepcidin and neutrophil gelatinase–associated lipocalin, nor did we measure urinary catalytic iron levels. The associations between catalytic iron and adverse outcomes could be confounded by a number of factors such as severity of illness or pRBC transfusions. However, in univariate analyses, catalytic iron levels were not associated with either comorbidities or status of the procedure (urgent versus elective), and the associations with adverse outcomes remained significant even after adjusting for age, enrollment eGFR, and number of pRBC transfusions. Nonetheless, residual confounding from unmeasured variables cannot be excluded.

Elevated plasma catalytic iron levels could be caused by decreased filtration rather than increased generation. However, iron is excreted mainly through sloughed mucosal cells in the gastrointestinal tract rather than in the urine. In addition, urinary catalytic iron levels are increased, not decreased, in patients with AKI (29). Finally, we found no correlation between eGFR and plasma catalytic iron levels. Nonetheless, we cannot exclude the possibility that among patients with severely diminished urine output, decreased excretion of catalytic iron could have contributed somewhat to elevated plasma levels.

Finally, we found that plasma catalytic iron levels correlated with plasma free hemoglobin levels, raising the possibility that the former could simply be an indirect (or downstream) marker of the latter. Although free hemoglobin is likely an important source of catalytic iron, free hemoglobin did not demonstrate an association with adverse outcomes, unlike catalytic iron. Importantly, the association between catalytic iron and adverse outcomes remained significant after adjusting for pRBC transfusions. These findings suggest that multiple sources are likely to contribute to elevated plasma catalytic iron levels and that catalytic iron may be a more direct mediator of AKI than free hemoglobin. Nonetheless, mechanisms by which iron could mediate AKI are complex and are likely to involve multiple pathways that may extend beyond catalytic iron. For example, these pathways may include toxicity mediated by heme- or myoglobin-bound iron (35), sources of iron that are not measured by the catalytic iron assay.

In conclusion, elevated plasma catalytic iron levels on arrival to the ICU were associated with a number of adverse outcomes, including AKI and death/RRT as well as hospital and 30-day mortality. Interventional strategies to reduce catalytic iron levels, such as iron chelation and minimization of pRBC transfusions, should be tested to minimize adverse outcomes among critically ill patients.

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Disclosures

S.S.W. reported serving as a consultant to CVS Caremark, BioTrends Research Group, Harvard Clinical Research Institute, and Takeda; providing expert testimony for GE Healthcare, Northstar Rx, and Salix; and receiving grants from the National Institute of Diabetes and Digestive Kidney Diseases, Otsuka, Merck, Genzyme, and Satellite Healthcare. M.R. and S.S.L. report holding a US patent for the methods and kit for measurement of serum catalytic iron for early detection of acute coronary syndrome and prediction of adverse cardiac events.

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