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Association of Ferritin, Transferrin, and TSAT with 1-Year Mortality in AMI Patients Admitted to the ICU: A MIMIC-IV Database Study

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Article

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Abstract

Background

The prognostic value of iron homeostasis markers—ferritin, transferrin, and transferrin saturation (TSAT)—in patients with acute myocardial infarction (AMI) remains poorly defined, particularly in critically ill populations requiring admission to the intensive care unit (ICU).

Methods

Patients with acute myocardial infarction (AMI) who underwent testing for iron homeostasis markers (ferritin, transferrin, and transferrin saturation [TSAT]) within 24 hours of ICU admission were included from the MIMIC-IV database. The primary outcome was one-year all-cause mortality. Multivariable Cox regression, Kaplan-Meier analysis, and restricted cubic spline models were employed to assess the associations of these three markers with mortality risk, with patients categorized into tertiles for grouped analyses. Receiver operating characteristic (ROC) curve analysis was performed to compare the predictive performance of the three markers for mortality and to evaluate their incremental predictive value beyond a baseline risk model.

Results

A total of 416 patients with AMI were included in the analysis. Using the lowest tertile as reference, the highest tertiles of ferritin (HR = 1.88) and TSAT (HR = 1.60) were independently associated with an increased risk of 1-year mortality, while the middle tertile of transferrin was associated with a reduced risk (HR = 0.64). Restricted cubic spline models suggested nonlinear associations. The predictive performance of each marker was limited (AUC range: 0.57–0.63), and none significantly improved the predictive ability of the baseline model.

Conclusion

Ferritin and TSAT measured within 24 hours of ICU admission, as well as decreased transferrin, are independent predictors of 1-year all-cause mortality in ICU-admitted patients with AMI. However, their incremental predictive value beyond traditional risk models is limited. Subgroup analyses suggest that the prognostic value of these markers may be heterogeneous in patients with specific comorbidities (e.g., COPD, AF, diabetes, and CKD), a finding that warrants further investigation.

I. Introduction

Acute Myocardial Infarction (AMI) remains a leading cause of mortality and disability globally. Despite notable progress in reperfusion therapies and secondary prevention strategies, The mortality rate among patients with acute myocardial infarction (AMI) remains high. [1, 2]. A deeper exploration of the pathogenesis of AMI, along with an understanding of its prognostic markers, is essential in identifying novel therapeutic and interventional approaches.

Iron is a vital trace element that participates in key physiological activities, including oxygen transportation and energy metabolism [3, 4]. Recent research indicates that iron exerts a dual effect within the cardiovascular system and other organ systems, due to its ability to catalyze redox reactions based on its valence states. This duality allows iron to maintain cellular homeostasis but also contributes to cytotoxicity under certain pathological conditions. In the heart, iron plays a critical role in molecular oxygen transport and cellular respiration; however, pathological accumulation can

induce cardiomyocyte death via dysregulated oxidative stress [5]. Emerging evidence implicates iron homeostasis imbalance as a driver of myocardial injury, functioning through mechanisms such as oxidative stress and inflammatory responses, ultimately impacting cardiovascular disease prognosis [6]. The identification of new mechanisms, such as ferroptosis, has further stimulated interest in the study of iron homeostasis and its related pathways in cardiovascular pathology.

Although numerous studies have highlighted links between iron homeostasis-related markers and cardiovascular disease [7–10], research to date has predominantly focused on heart failure cohorts. While mechanistic studies have suggested a relationship between iron homeostasis and coronary artery disease, the precise association with AMI—particularly concerning readily available clinical markers such as Ferritin, Transferrin, and Transferrin Saturation (TSAT)—remains insufficiently defined, especially regarding their prognostic value in AMI patients.

Ferritin serves as the principal intracellular iron-storage protein and is widely regarded as a reliable biomarker for assessing iron reserves, playing an important role in diagnosing iron deficiency. Notably, Ferritin acts as an acute-phase reactant, with levels increasing during decompensated states. This is clinically relevant, as extensive literature discusses the importance of acute-phase biomarkers for both the acute and chronic phases of cardiovascular disease [11, 12].

Transferrin, the main iron-transport protein in plasma, is influenced by iron status, systemic inflammation, and nutritional state. In iron deficiency, elevated Transferrin levels serve to augment iron transport capacity; conversely, inflammatory states may suppress Transferrin synthesis. Evidence suggests that routinely assessed markers such as serum iron, Transferrin, and TSAT outperform Ferritin in the diagnosis of inflammatory anemia among critically ill individuals [13].

Transferrin Saturation (TSAT) is a crucial metric for evaluating systemic iron metabolism, calculated as the ratio of serum iron concentration to Total Iron-Binding Capacity (TIBC), multiplied by 100%, reflecting the percentage of Transferrin bound by iron. Multiple previous studies report that decreased TSAT and Ferritin levels may directly indicate myocardial iron deficiency, which associates with adverse outcomes in coronary artery disease, while elevated Ferritin and Transferrin levels may contribute to coronary risk through metabolic and inflammatory pathways [14–17]. However, conflicting data have been presented in other studies, and several investigations have failed to confirm a definitive association [18–21].

Numerous studies have demonstrated that elevated iron homeostasis markers, particularly ferritin—serving as indicators of inflammation and iron metabolic dysregulation—are significantly associated with increased mortality across a range of critical illnesses, including internal medicine inpatients, severe trauma, ARDS, and severe COVID-19. This association is especially pronounced for admission measurements, underscoring their broad prognostic value. [22–24]

In summary, comprehensive investigation is required to fully elucidate the complex relationships between iron-homeostasis indices and clinical outcomes in patients with acute myocardial infarction in the ICU. Accordingly, the principal aim of this study is to assess the correlation between commonly assessed clinical iron-homeostasis markers (Ferritin, Transferrin, TSAT) during the acute phase and the prognosis of AMI patients in the ICU, and to compare their respective prognostic efficacies. These findings are expected to inform risk stratification, enabling clinicians to identify high-risk subgroups early in the hospitalization course, thereby facilitating individualized treatment and monitoring strategies.

II. Research Methods

2.1 Database

This study utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV v3.0) database, comprising over 50,000 intensive care unit (ICU) admissions collected at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, spanning from 2008 to 2022. The MIMIC-IV database provides extensive datasets, including patient demographics, vital signs, laboratory data, as well as diagnoses encoded in accordance with the International Classification of Diseases Ninth Revision (ICD-9) and Tenth Revision (ICD-10) systems.

2.2 Research Population

Patients were identified from the MIMIC-IV database using the following criteria: diagnosis of Acute Myocardial Infarction (ICD-9 codes beginning with 410 or ICD-10 codes beginning with I21). Only the first ICU admission for each patient during the study period was considered. Inclusion required the presence of complete iron-homeostasis data (serum iron, Ferritin, Transferrin, TIBC) obtained within the first 24 hours of ICU admission. For patients with multiple records, the earliest was selected. Exclusion criteria comprised ICU stay duration less than 24 hours, age younger than 18 years, and incomplete dataset entries. Ultimately, 416 cases were identified. Based on clinical experience and prior research, given that both elevated and reduced levels of iron homeostasis markers may influence patient prognosis, patients were stratified into low, medium, and high groups according to tertiles of the exposure variable, following established study protocols [11].

2.3 Data Extraction and Variables

Data were extracted using Structured Query Language (SQL) with PostgreSQL, capturing patients' baseline characteristics spanning demographics (age, sex, height, weight), vital signs (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP]), and severity scores at admission (including Simplified Acute Physiology Score II [SAPSII], Systemic Inflammatory Response Syndrome [SIRS] score, Acute Physiology Score III [APSIII], and Sequential Organ Failure Assessment [SOFA] score). Medication histories (e.g., β-blockers, loop diuretics [including furosemide and torsemide], angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB]), laboratory parameters (red blood cells [RBC], white blood cells [WBC], neutrophils, hemoglobin, lymphocytes, platelets, urinary creatinine [Ucr], serum creatinine [Scr], blood urea nitrogen [BUN], creatine kinase-MB [CKMB], partial pressure of carbon dioxide [PCO2], C-reactive protein [CRP], total cholesterol [TC], total triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], NT-proBNP, low-density lipoprotein cholesterol [LDL-C], potassium, sodium, pH, PO2, glucose, HbA1c, and TnT), and iron metabolism indicators (serum iron, Ferritin, Transferrin, TIBC) were collected within the initial 24 hours after ICU admission. For repeated laboratory measures, the earliest value was analyzed. Comorbid conditions (chronic obstructive pulmonary disease [COPD], atrial fibrillation [AF], diabetes, and CKD) were identified utilizing ICD-10 and ICD-9 codes. The observation period extended from ICU admission until the occurrence of the primary endpoint.

The Transferrin Saturation (TSAT) was calculated using the formula: TSAT (%) = serum iron (μg/dL) / total iron-binding capacity (μg/dL) × 100.

Among the variables included in this study, those with a missing rate exceeding 50% were excluded from the final analysis. For variables with a missing rate below 50%, the missing values were considered potentially not missing completely at random. To maximize the sample size and reduce potential bias that might arise from simply deleting cases with missing data (complete-case analysis), we employed multiple imputation to handle the missing values.

III. Statistical Methods

Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate, and were compared between groups using either the Mann-Whitney U test or the Student's t-test, based on variable distribution. Categorical variables are described by frequency and proportion (%) and were compared using either Fisher's exact test or Pearson's chi-square test, depending on the sample characteristics.

Following stratification into tertile groups, Kaplan-Meier survival analysis was employed to compare mortality among categories. Associations between Ferritin, Transferrin, TSAT, and 1-year mortality were estimated using the Cox proportional-hazards model, yielding adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Model 1 assessed unadjusted associations; Model 2 was adjusted for sex, age, and Body Mass Index (BMI); and Model 3 incorporated all covariates in Model 2, plus variables with $p < 0.05$ in the baseline characteristics (SBP, SAPSII, SOFA, APSIII, RBC, WBC, hemoglobin, Scr, BUN, ACEI, AF). Ferritin, Transferrin, and TSAT were each included as continuous and categorical predictors. HRs with 95% CIs were reported. Model fit and multicollinearity were assessed by likelihood-ratio testing and variance inflation factor, respectively. For all indicators, the lowest tertile served as the reference group.

The predictive performance of each marker was further assessed using Receiver Operating Characteristic (ROC) curve and Area Under Curve (AUC) analyses. Optimal cut-off values were determined. A basic risk model was constructed using variables with $P < 0.05$ in baseline characteristics, and each marker was added to this model to evaluate its incremental predictive value.

Sensitivity Analysis and Exploratory Analysis

To evaluate the robustness of the findings, Ferritin, Transferrin, and TSAT were categorized into high and low groups based on the optimal cut-off values derived from ROC analysis, and Cox regression analyses were subsequently repeated.

Restricted cubic spline models were employed to assess potential dose–response relationships and nonlinear trends between each marker and 1-year mortality.

Furthermore, based on the aforementioned cut-off values, subgroup analyses were performed according to age (dichotomized by median), sex, COPD, AF, diabetes, and CKD status. Cox proportional hazards models were used to calculate HRs and 95% CIs for mortality risk within each subgroup, and interactions were rigorously tested using the likelihood-ratio test.

All statistical analyses were conducted using R software (version 4.5.0) and SPSS. A two-sided P value < 0.05 was considered statistically significant.

IV. Results

4.1 Baseline Characteristics

After screening eligible AMI cases from the MIMIC-IV database, a total of 416 patients who met all inclusion criteria were ultimately included in this study. The flow of patient selection is outlined in Figure 1. Patients were grouped according to 1-year survival status, resulting in a survival group (n = 222) and a non-survival group (n = 194). Compared with survivors, non-survivors were older and had higher disease severity scores at admission. Non-survivors also exhibited lower RBC, SBP, and hemoglobin, but higher WBC, Scr, and BUN. The prevalence of AF was increased, while ACEI usage was decreased in the non-survival group. Importantly, non-survivors demonstrated significantly elevated Ferritin and TSAT, as well as lower Transferrin and TIBC, in contrast to the survival group, whereas differences in serum iron were not statistically significant. Given the approximate equivalence between TIBC (μg/dL) and serum Transferrin

concentration (mg/dL) × 1.25, subsequent analyses prioritized Ferritin, Transferrin, and TSAT. A comprehensive comparison of baseline characteristics is provided in Table 1.

Table 1

4.2 Association between Ferritin and 1-Year Death Risk

When Ferritin was evaluated as a continuous variable, Cox proportional-hazards Model 1 (HR 1.00; 95% CI 1.00–1.00; P = 0.656) and Model 2 (HR 1.00; 95% CI 1.00–1.00; P = 0.439) showed no significant association with 1-year mortality. This non-significance persisted in Model 3 (HR 1.00; 95% CI 1.00–1.00; P = 0.208).

Patients were classified into tertiles according to Ferritin level: T1 (reference), T2, and T3. Kaplan–Meier survival curves demonstrated significant mortality differences across tertiles (P< 0.001, see Figure 2). In Cox regression analyses, compared with T1, T2 was significantly associated with increased mortality in Model 1 (HR 1.72; 95% CI 1.18–2.52; P = 0.005), Model 2 (HR 1.80; 95% CI 1.23–2.64; P = 0.003), and Model 3 (HR 1.54; 95% CI 1.03–2.30; P = 0.036). Similarly, T3 showed significantly higher risk in Model 1 (HR 2.48; 95% CI 1.72–3.59; P < 0.001), Model 2 (HR 2.76; 95% CI 1.90–4.00; P < 0.001), and Model 3 (HR 1.88; 95% CI 1.23–2.87; P = 0.004).

The restricted cubic spline (RCS) model depicted a non-linear association between Ferritin and 1-year mortality, with a significant overall association (P for overall = 0.005) and non-linearity (P for nonlinear = 0.019). As Ferritin levels increased, the risk of mortality began to rise at lower concentrations, with the Hazard Ratio (HR) showing a progressive increase. Excess risk was observed even at moderate Ferritin levels, and this elevated risk persisted at higher concentrations (see Figure 3).

4.3 Association between Transferrin and 1-Year Death Risk

Considering Transferrin as a continuous predictor, Cox proportional-hazards Models 1 (HR 0.99; 95% CI 0.99–0.99; P < 0.001), 2 (HR 0.99; 95% CI 0.99–0.99; P < 0.001), and 3 (HR 0.99; 95% CI 0.99–0.99; P = 0.007) all indicated a significant inverse association with 1-year mortality.

Stratification by Transferrin tertiles yielded groups T1 (reference), T2, and T3. Kaplan–Meier survival analysis revealed significant mortality differences across groups (P < 0.001, Figure 2). Compared with T1, T2 was associated with significantly lower mortality in Model 1 (HR 0.54; 95% CI 0.38–0.75; P < 0.001), Model 2 (HR 0.52; 95% CI 0.37–0.73; P < 0.001), and Model 3 (HR 0.64; 95% CI 0.45–0.91; P = 0.013). T3 also showed significantly lower risk in Model 1 (HR 0.48; 95% CI 0.34–0.68; P < 0.001) and Model 2 (HR 0.47; 95% CI 0.33–0.67; P < 0.001), but the association was attenuated and became non-significant in Model 3 (HR 0.68; 95% CI 0.46–1.02; P = 0.062).

The RCS analysis identified a non-linear relationship (nonlinear P = 0.003); HRs exceeded 1 for Transferrin <150, then rapidly decreased to below 1 as Transferrin increased above 200, indicating reduced risk (Figure 3).

4.4 Association between Transferrin Saturation and 1-year Mortality Risk

When Transferrin Saturation (TSAT) was entered as a continuous variable, Cox proportional-hazards Model 1 (HR 1.01; 95% CI 1.01–1.01; P < 0.001) and Model 2 (HR 1.01; 95% CI 1.01–1.01; P < 0.001) showed significant associations with 1-year mortality; however, no statistically significant association was found in the fully adjusted Model 3 (HR 1.00; 95% CI 1.00–1.01; P = 0.191).

Tertile-based analyses assigned patients to T1 (reference), T2, and T3. Kaplan–Meier survival analysis indicated significant mortality differences across TSAT groups (*p* = 0.034, Figure 2). Compared with T1, T2 was not significantly associated with mortality in Model 1 (HR 1.24; 95% CI 0.87–1.78; P = 0.234) or Model 2 (HR 1.30; 95% CI 0.90–1.86; P =

0.159), but became significant in Model 3 (HR 1.61; 95% CI 1.11–2.34; P = 0.012). T3 showed significantly higher risk in all models: Model 1 (HR 1.59; 95% CI 1.11–2.26; P = 0.011), Model 2 (HR 1.69; 95% CI 1.19–2.42; P = 0.004), and Model 3 (HR 1.60; 95% CI 1.10–2.34; P = 0.014).

The RCS model showed a linear trend between TSAT and mortality (non-linearity P = 0.395). Mortality risk consistently increased as TSAT rose, particularly at values >50% (Figure 3).

Figure 2

Table 2

Figure 3

4.5 ROC Curve Analysis of Ferritin, Transferrin, and Transferrin Saturation

Receiver Operating Characteristic (ROC) curves were constructed to assess the predictive accuracy of Ferritin, Transferrin, and TSAT for 1-year mortality in patients with severe AMI (Figure 4). The AUCs were 0.63 (95% CI: 0.57–0.68) for Ferritin, 0.62 (95% CI: 0.56–0.67) for Transferrin, and 0.57 (95% CI: 0.51–0.62) for TSAT; no statistically significant pairwise differences were found. The optimal thresholds determined were 196.5 for Ferritin, 131.5 for Transferrin, and 40.0 for TSAT. When the three markers were incorporated into a base risk model (containing age, SBP, SAPSII, SOFA, APSIII, RBC, WBC, hemoglobin, SCr, BUN, ACEI, AF), incremental improvements in prediction were not statistically significant, as reflected by the corresponding p-values for the AUCs in Figure 4. This indicates that the addition of iron homeostasis indicators did not meaningfully enhance the discriminative ability of standard risk models for AMI prognosis. (AUC: basic model 0.738 (95%CI: 0.691−0.786) vs. basic model + ferritin 0.742 (95%CI: 0.695−0.789) p = 0.3938, basic model + transferrin 0.741 (95%CI: 0.694−0.788) p = 0.7272, basic model + TAST (95%CI: 0.693−0.787) p = 0.5268).

Figure 4

4.6 Sensitivity and Exploratory Analysis

To assess the robustness and reliability of the findings, variance inflation factor (VIF) analysis was performed on the fully adjusted Model 3, and all VIF values for iron homeostasis markers were < 2.5, indicating no significant collinearity. Furthermore, grouping analyses based on optimal cut-off values derived from ROC analysis were conducted, and the results remained consistent with the main analysis. Kaplan-Meier survival curves and Cox regression outputs are detailed in Supplementary Table 3 and Figure 5.

Subgroup analyses evaluated the associations between iron homeostasis markers and 1-year mortality across different comorbidity strata. Interaction analyses revealed significant interactions for ferritin in patients with COPD and AF, for transferrin in patients with diabetes, and for TSAT in patients with CKD. In all other subgroups, the 1-year mortality risks were consistent with the overall findings, and no significant interactions were observed (Table 4). These findings underscore the prognostic value of iron homeostasis markers in specific patient subgroups and highlight the heterogeneity of risk associations across different comorbidity profiles.

Table 4

V. Discussion

This study systematically evaluated the association between iron homeostasis markers obtained within 24 hours of ICU admission and clinical outcomes in patients with acute myocardial infarction (AMI) in the intensive care unit using

the MIMIC-IV database. The results showed that ferritin, transferrin, and transferrin saturation (TSAT) were significantly associated with 1-year mortality risk, suggesting that these early iron homeostasis markers hold potential value for early identification of high-risk patients and risk stratification. These findings provide novel prognostic evidence to support individualized management of AMI patients in the ICU setting.

5.1 Relationship between Ferritin and Prognosis in AMI Patients

The findings indicate that elevated serum Ferritin is independently associated with an increased risk of 1-year mortality following AMI. In tertile-based analyses, patients in the highest Ferritin group (>577.10) had a 1.88-fold (95% CI: 1.23–2.87) higher risk of death compared to those in the lowest group (<172.95), after extensive adjustment in Model 3. The restricted cubic spline model further delineated a non-linear relationship (P for nonlinear < 0.05), demonstrating a significantly heightened mortality risk at higher Ferritin concentrations.

Ferritin is an established biomarker of body iron stores, yet its interpretation in acute settings is complicated by its dual role as an iron-storage protein and an acute-phase reactant[12]

While elevated ferritin has been linked to coronary artery disease risk, its prognostic value in AMI remains controversial [14, 25-27]. In line with prior studies in ischemic heart disease [11]. we found that high ferritin levels independently predicted 1-year mortality in ICU-admitted AMI patients. Specifically, ferritin >577.10 ng/mL was associated with an 1.88-fold increased risk, consistent with threshold effects reported at >323 ng/mL post-MI [28] and >316 ng/mL in acute coronary syndrome [27]. Mechanistically, iron overload may exacerbate myocardial damage via oxidative stress, ferroptosis, and mitochondrial dysfunction [28-30]. These pathways are likely amplified in the ICU setting, where patients experience both acute ischemic insult and systemic inflammation. Importantly, while previous studies have emphasized the adverse effects of **low** ferritin [20, 21],our findings underscore the prognostic significance of high ferritin. This divergence may reflect differences in study populations and timing of measurement: our cohort consisted exclusively of critically ill AMI patients with ferritin assessed within 24 hours of ICU admission, a period marked by maximal inflammatory and stress responses.

5.2 Relationship between Transferrin and Prognosis in AMI Patients

This study demonstrated a significant inverse association between serum transferrin levels and 1-year mortality in ICU-admitted patients with AMI. When analyzed as a continuous variable, higher transferrin levels were consistently associated with a significantly lower risk of death across all regression models. In categorical analyses, patients in the middle tertile (T2) showed a significantly reduced mortality risk in the fully adjusted model (HR: 0.64, 95% CI: 0.45–0.91). The protective association for the highest tertile (T3), although attenuated and not statistically significant (HR: 0.68, 95% CI: 0.46–1.02, P = 0.062), still suggested a potential protective trend. Restricted cubic spline analysis further confirmed a non-linear relationship (P = 0.003): mortality risk increased substantially when transferrin was below 150 mg/dL, decreased rapidly once levels exceeded the 150–200 mg/dL range, and remained below baseline after surpassing 200 mg/dL, with no further dose-dependent enhancement. This non-linear pattern indicates that the protective effect of transferrin emerges at moderate concentrations and reaches a plateau beyond a certain threshold. The lack of statistical significance in the T3 group may be attributable to limited sample size, over-adjustment in the multivariable model, or a higher burden of confounders in this subgroup (the median transferrin level in the T3 group was 206 mg/dL, exceeding the 200 mg/dL threshold). Of note, given the observational nature of this study, causality cannot be inferred; reduced transferrin levels are more likely to serve as a composite marker of inflammatory burden, nutritional depletion, and functional iron deficiency, reflecting poorer overall clinical status.

As the principal iron transport protein, transferrin deficiency impairs the delivery of iron required for erythropoiesis and tissue oxygenation, thereby exacerbating myocardial hypoxia. Transferrin is also a negative acute-phase reactant[13,

31], its synthesis is suppressed under inflammatory conditions, leading to decreased circulating levels. Such downregulation disrupts cellular iron uptake and compromises both cardiomyocyte and endothelial cell function [32]. Accordingly, the reduced transferrin levels observed in our study likely reflect a confluence of inflammation and functional iron deficiency, manifesting as impaired myocardial metabolism and compromised repair capacity. Although these pathophysiological mechanisms are biologically plausible, clinical evidence regarding the independent prognostic value of transferrin in AMI patients has remained limited. Our study addresses this gap and provides novel evidence supporting transferrin as a potential risk stratification tool in ICU-admitted AMI patients.

5.3 Relationship between Transferrin Saturation and Prognosis in AMI Patients

Our analysis revealed a complex association between Transferrin Saturation (TSAT) and 1-year mortality risk in AMI patients. When modeled as a continuous variable, the association was significant in initial models but was attenuated and lost statistical significance in the fully adjusted model (HR: 1.00; 95% CI: 1.00–1.01; P = 0.191). However, tertile-based analysis revealed that patients in the highest TSAT tertile (T3) remained at a significantly increased risk of mortality even after full adjustment (HR: 1.60; 95% CI: 1.10–2.34; P = 0.014).Restricted cubic spline analysis showed a generally linear relationship (p = 0.395), with risk increasing as TSAT rose beyond 50%. TSAT, reflecting the proportion of Transferrin bound by iron, is an established indicator of iron metabolism status. High TSAT may indicate systemic iron overload, a condition known to be associated with exacerbated oxidative stress and myocardial injury [28-30]. However, in the context of acute inflammation, elevated TSAT can also be driven by a rapid decline in transferrin levels, and thus may not be fully equivalent to classical iron overload. In this study, the association between TSAT as a continuous variable and mortality was attenuated and lost significance after full adjustment, suggesting that its effect may be partially confounded by inflammatory, nutritional, or renal factors. Notably, prior studies have consistently identified low TSAT as an independent predictor of mortality in elderly and heart failure populations [33, 34]. The contrast between those findings and ours likely stems from fundamental differences in clinical settings and patient profiles. Our cohort consisted of critically ill AMI patients in the ICU, where dysregulated iron metabolism is predominantly driven by inflammation and acute stress, rather than by chronic iron deficiency. In this specific population, high TSAT may more directly reflect relative iron excess, heightened oxidative stress, and increased susceptibility to reperfusion injury—rather than serving as a reassuring indicator of sufficient iron stores. These findings underscore that the clinical interpretation of TSAT and other iron metabolism markers is highly population-dependent. In ICU-admitted AMI patients, elevated TSAT during the early phase of admission—particularly exceeding 50%—should be regarded as a high-risk warning signal rather than a benign indicator of adequate iron status. Applying iron metabolism assessment frameworks derived from heart failure or community-based populations to this setting may underestimate the prognostic risk.

5.4 Comparison of Predictive Values and Subgroup Analysis

ROC analysis showed that ferritin, transferrin, and TSAT demonstrated comparable predictive performance for 1-year mortality in patients with AMI, with AUCs of 0.63 (95% CI: 0.57–0.68), 0.62 (95% CI: 0.56–0.67), and 0.57 (95% CI: 0.51–0.62), respectively, and no statistically significant differences between any pairwise comparisons. The optimal cut-off values identified—196.5 μg/L for ferritin, 131.5 mg/dL for transferrin, and 40.0% for TSAT—may serve as preliminary references for rapid identification of high-risk individuals; however, given their limited predictive accuracy when used alone, they should be applied cautiously as standalone thresholds for clinical decision-making.

Notably, the addition of these markers to a baseline model incorporating established risk factors did not significantly improve predictive discrimination. This finding suggests, on one hand, substantial information overlap between iron homeostasis markers and existing covariates (e.g., inflammatory and renal parameters, illness severity scores), with

their prognostic effects likely mediated by strong risk predictors such as SAPSII, SOFA, and Scr. On the other hand, it also reflects the inherent limitations of single admission measurements in predicting long-term outcomes.

Nevertheless, subgroup analyses revealed that the prognostic significance of these markers varied substantially by comorbid condition. Significant interactions were observed for ferritin in patients with COPD and AF, for transferrin in those with diabetes, and for TSAT in those with CKD. These findings underscore the context-dependent nature of iron metabolism in determining clinical outcomes. In COPD, AF, and diabetes, chronic systemic inflammation and oxidative stress may potentiate the acute-phase reactivity of ferritin and transferrin, thereby amplifying their association with mortality. In CKD, by contrast, impaired renal handling of iron—manifesting as reduced erythropoietic drive, increased hepcidin, and urinary transferrin loss—may specifically distort the relationship between TSAT and survival.

Together, these observations indicate that although the incremental predictive value of iron homeostasis markers is limited in the overall AMI population, they may still hold important risk stratification utility in selected clinical subgroups —particularly in patients with coexisting COPD, AF, diabetes, or CKD. This heterogeneity reinforces the need for population-specific interpretation of iron metabolism markers in ICU-admitted AMI patients and warrants further investigation to validate their prognostic role in these high-risk subsets.

Multivariable and subgroup analyses provide robust evidence for an independent association between serum ferritin, transferrin, and TSAT levels and the risk of 1-year all-cause mortality in patients with AMI. Mechanistically, the impact of iron metabolic dysregulation on myocardial injury involves two distinct yet interrelated pathophysiological pathways.

Pathway I: Direct toxicity of iron overload. In patients with true iron excess, labile iron catalyzes the generation of reactive oxygen species via the Fenton reaction, triggering oxidative stress, lipid peroxidation, and mitochondrial dysfunction, thereby initiating ferroptosis—an iron-dependent form of regulated cell death[28-30] [35-37]. Iron overload may also promote vascular calcification and dysregulate immune-inflammatory responses, further exacerbating myocardial injury. Given the heart's limited regenerative capacity, irreversible loss of functional cardiomyocytes induced by iron overload translates into sustained cardiac dysfunction.

Pathway II: Phenotypic expression of the acute-phase response. Ferritin and transferrin are classic acute-phase proteins whose circulating levels can be markedly elevated or suppressed by inflammatory cytokines (e.g., IL-6) in the absence of true alterations in iron stores. In this context, hyperferritinemia does not signify iron overload but rather reflects systemic inflammatory burden; conversely, hypotransferrinemia is less indicative of iron deficiency than of inflammation-driven synthesis inhibition and nutritional depletion [38]. These biomarkers may independently exacerbate myocardial injury by amplifying oxidative stress and impairing endothelial function.

In critically ill AMI patients admitted to the ICU, these two pathways are not mutually exclusive but are highly intertwined. This population is simultaneously exposed to multiple insults, including acute ischemia-reperfusion injury, systemic inflammatory response syndrome, and multiorgan dysfunction. On one hand, the burst of reactive oxygen species triggered by ischemia-reperfusion directly induces cardiomyocyte ferroptosis. On the other hand, the robust inflammatory storm drives acute-phase responses, leading to rapid fluctuations in ferritin and other iron homeostasis markers. Consequently, even in the absence of classical chronic iron overload, patients may exhibit a "pseudo-iron overload" phenotype (e.g., passively elevated TSAT), which nonetheless carries significant prognostic information.

This population specificity provides a pathophysiological rationale for the key findings of our study. Previous studies in heart failure or community-dwelling elderly populations identified low TSAT as a risk factor for adverse outcomes, reflecting a risk pathway dominated by chronic iron deficiency. In contrast, our study demonstrates that in ICU-admitted AMI patients, high TSAT is independently associated with increased mortality—underscoring the dominance of "relative iron excess" under conditions of acute inflammatory stress. Similarly, the prognostic value of ferritin and transferrin in

this population derives more from their role as readouts of acute-phase burden than from their conventional interpretation as markers of iron stores.

In summary, the prognostic interpretation of iron homeostasis markers in ICU-admitted AMI patients must move beyond the traditional "iron deficiency vs. overload" dichotomy and adopt a multidimensional framework that integrates inflammatory load, acute stress, and organ dysfunction. This conceptual advance also provides a theoretical foundation for future interventional studies targeting the crosstalk between iron metabolism and inflammatory pathways.

5.5 Significance and limitations of the study

This study systematically evaluated the association between iron homeostasis markers—ferritin, transferrin, and transferrin saturation (TSAT)—measured within 24 hours of ICU admission and clinical outcomes in patients with acute myocardial infarction (AMI), addressing a gap in prior research that predominantly focused on heart failure cohorts. The findings identified elevated ferritin, elevated TSAT, and reduced transferrin as independent predictors of adverse prognosis in this specific population. These results suggest that iron metabolism parameters obtained early after admission—readily available in routine clinical practice—may serve as useful adjuncts for early risk stratification in ICU-admitted AMI patients and warrant further investigation into their potential role in guiding individualized management strategies.

Several important limitations of this study should be acknowledged. First, the retrospective cohort design precludes definitive causal inferences regarding the relationship between iron homeostasis markers and clinical outcomes. Despite extensive multivariable adjustment, the possibility of residual confounding cannot be entirely excluded. Second, to capture iron metabolism status prior to complex interventions, we required all included patients to have a complete panel of iron metabolism tests performed within 24 hours of ICU admission. While this criterion ensures the assessment of early iron homeostasis disturbance, it also introduced selection bias by systematically excluding patients who were too critically ill to undergo timely testing or those with incomplete data. This may have reduced the final sample size (n = 416) and potentially limited statistical power and population representativeness. Third, reliance on single time-point measurements at admission—while avoiding confounding from subsequent treatments—precludes insight into the temporal dynamics of iron metabolism during the acute phase and their prognostic implications. Most importantly, the study population was exclusively derived from ICU settings; therefore, our findings are not generalizable to all AMI patients and should be interpreted as applicable primarily to critically ill individuals requiring intensive care. Future multicenter, prospective studies are warranted to validate these associations in broader AMI populations and to explore whether dynamic monitoring of iron parameters or targeted iron-modulating interventions can improve clinical outcomes.

5.6 Outlook

Future research should prioritize multicenter, prospective designs to further elucidate the dynamic trajectories of iron homeostasis markers and their prognostic implications across the full spectrum of AMI patients—not limited to critically ill populations in the ICU setting. Concurrent mechanistic investigations are warranted to clarify the precise pathophysiological roles of these markers in myocardial injury. Interventional trials targeting iron metabolism abnormalities hold promise for developing novel therapeutic strategies applicable to broader AMI cohorts. Additionally, exploring the integration of iron homeostasis markers into established AMI risk scoring systems, as well as developing individualized management protocols based on patient-specific iron metabolism profiles, represents a valuable avenue for clinical translation. Such multicenter, prospective studies will help validate and extend our findings, enhancing their generalizability and clinical applicability.

5.7 Conclusion

This study provides the first systematic evaluation of the association between iron homeostasis markers—ferritin, transferrin, and transferrin saturation (TSAT)—measured within 24 hours of ICU admission and prognosis in patients with acute myocardial infarction (AMI), addressing a key research gap left by prior studies that predominantly focused on heart failure. Our findings demonstrate that elevated ferritin, elevated TSAT, and reduced transferrin are independent predictors of 1-year all-cause mortality in this population, highlighting the importance of assessing iron metabolism parameters for early risk stratification in critically ill AMI patients. The prognostic cut-off values identified in this study—196.5 μg/L for ferritin, 131.5 mg/dL for transferrin, and 40.0% for TSAT—may serve as preliminary references for identifying high-risk individuals in future research; however, their clinical utility as standalone screening thresholds requires validation in prospective studies. Subgroup analyses further revealed that the prognostic significance of these markers varied substantially by comorbid condition, with pronounced interactions observed in patients with COPD, AF, diabetes, and CKD, underscoring the population-dependent nature of iron dysregulation. Mechanistically, the interplay between direct iron overload toxicity and phenotypic expression of the acute-phase response provides a plausible explanation for the risk associations observed in this unique ICU-AMI population. Nevertheless, as a retrospective, single-center study, our findings are subject to inherent limitations including selection bias, residual confounding, and the inability to capture dynamic changes in iron metabolism from single admission measurements. Future multicenter prospective studies are warranted to validate these findings, investigate the prognostic value of longitudinal iron parameter monitoring, and evaluate whether interventions targeting iron metabolism pathways may improve outcomes in patients with AMI.

Abbreviations

ICU
Intensive Care Unit
AMI
Acute Myocardial Infarction
MIMIC-IV
Medical Information Mart for Intensive Care IV
ROC
Receiver Operating Characteristic
TSAT
Transferrin Saturation
TIBC
Total Iron-Binding Capacity
ICD-9
International Classification of Diseases Ninth Revision
ICD-10
International Classification of Diseases Tenth Revision
SQL
Structured Query Language
HR
Heart Rate
SBP
Systolic Blood Pressure
DBP

Diastolic Blood Pressure
SAPSII
Simplified Acute Physiology Score II
SIRS
Systemic Inflammatory Response Syndrome
APSIII
Acute Physiology Score III
SOFA
Sequential Organ Failure Assessment
ACEI
Angiotensin-Converting Enzyme Inhibitors
ARB
Angiotensin Receptor Blockers
RBC
Red Blood Cells
WBC
White Blood Cells
Ucr
Urinary Creatinine
Scr
Serum Creatinine
BUN
Blood Urea Nitrogen
CKMB
Creatine Kinase-MB
PCO2
Partial Pressure of Carbon Dioxide
CRP
C-Reactive Protein
TC
Total Cholesterol
TG
Total Triglycerides
HDL-C
High-Density Lipoprotein Cholesterol
NT-proBNP
N-terminal pro-B-type Natriuretic Peptide
LDL-C
Low-Density Lipoprotein Cholesterol
PO2
Partial Pressure of Oxygen
HbA1c
Glycated Hemoglobin
TnT
Troponin T
COPD

Chronic Obstructive Pulmonary Disease
AF
Atrial Fibrillation
CKD
Chronic Kidney Disease
SD
Standard Deviation
IQR
Interquartile Range
HR
Hazard Ratio(Note:The abbreviation is the same as "Heart Rate," but it has different meanings in different contexts)
CI
Confidence Interval
BMI
Body Mass Index
AUC
Area Under Curve
VIF
Variance Inflation Factor
RCS
Restricted Cubic Spline

Declarations

Ethics approval and consent to participate

Patient consent was not required for this study as the use of this de-identified database has been approved by the Institutional Review Boards of both the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Upon successful completion of the necessary evaluation (Certificate No. 32173796), the individuals involved in this study were granted authorization to access the MIMIC-IV database after completing a series of courses provided by the National Institutes of Health (NIH).

Consent for publication

Not Applicable.

Availability of data and materials

The data underlying this article were derived from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (version 3.0), which is available in the PhysioNet repository at https://physionet.org/content/mimiciv/3.0/. Researchers can access the database after completing the required training course (CITI Data or Specimens Only Research) and signing a data use agreement, following the protocol detailed on the PhysioNet website.

Competing Interests

None declared.

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Authors' contributions

Yubin Shen: Study concept and design. Yubin Shen, Chenyang Wu, Yuqin Zhan, Tingshan Yu: Acquisition, analysis, or interpretation of data. Yubin Shen: Drafting of the manuscript. All authors: Critical revision of the manuscript for important intellectual content. Yubin Shen, Yuqin Zhan: Statistical analysis. Chenyang Wu, Tingshan Yu: Administrative, technical, or material support.Yahui Ding: Study supervision.

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Clinical trial number

Not Applicable.

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Tables

Table 1

Variables	Total (n = 416)	0 (n = 222)	1 (n = 194)	P
Age, M (Q_1, Q_3)	69.50 (59.00, 78.00)	67.00 (57.00, 75.00)	73.00 (64.00, 80.00)	<.001
Bmi, M (Q_1, Q_3)	27.38 (24.69, 31.24)	27.52 (24.80, 31.34)	27.24 (24.37, 31.01)	0.571
Heart Rate, M (Q_1, Q_3)	103.00 (90.00, 117.25)	102.00 (89.25, 115.00)	105.00 (92.00, 119.75)	0.253
Sbp, M (Q_1, Q_3)	143.00 (128.00, 159.00)	147.00 (130.00, 162.00)	139.00 (125.00, 155.75)	0.003
Dbp, M (Q_1, Q_3)	89.00 (78.00, 102.00)	89.00 (80.00, 102.00)	90.00 (78.00, 101.75)	0.613
Sapsii, M (Q_1, Q_3)	39.50 (32.00, 49.00)	36.00 (29.00, 43.00)	45.50 (38.00, 54.00)	<.001
Sofa, M (Q_1, Q_3)	6.00 (3.00, 8.00)	5.00 (2.25, 8.00)	6.00 (4.00, 9.00)	<.001
Apsiii, M (Q_1, Q_3)	48.00 (39.00, 64.00)	44.50 (34.00, 57.00)	54.00 (43.00, 70.50)	<.001
Rbc, M (Q_1, Q_3)	3.23 (2.82, 3.74)	3.35 (2.90, 3.79)	3.10 (2.74, 3.66)	0.004
Wbc, M (Q_1, Q_3)	12.20 (8.70, 16.15)	11.70 (8.45, 15.47)	12.60 (8.95, 17.98)	0.042
Hemoglobin, M (Q_1, Q_3)	9.40 (8.30, 11.00)	9.70 (8.50, 11.10)	9.20 (8.20, 10.78)	0.016
Platelets, M (Q_1, Q_3)	214.00 (152.75, 280.00)	217.00 (163.25, 276.75)	207.00 (143.00, 284.75)	0.292
Scr, M (Q_1, Q_3)	1.80 (1.08, 3.30)	1.50 (0.93, 2.90)	2.10 (1.20, 3.60)	<.001
Bun, M (Q_1, Q_3)	38.00 (23.00, 64.25)	33.00 (20.00, 59.00)	44.00 (29.00, 67.00)	<.001
Ckmb, M (Q_1, Q_3)	14.00 (5.00, 35.25)	15.00 (6.00, 44.00)	12.50 (5.00, 29.75)	0.221
Pco2, M (Q_1, Q_3)	44.90 (39.00, 51.00)	44.90 (39.25, 51.45)	44.90 (39.00, 51.00)	0.883
Potassium, M (Q_1, Q_3)	4.50 (4.10, 5.10)	4.50 (4.10, 5.00)	4.50 (4.10, 5.20)	0.531
Sodium, M (Q_1, Q_3)	139.00 (136.00, 142.00)	140.00 (137.00, 142.00)	139.00 (136.00, 142.00)	0.061
Ph, M (Q_1, Q_3)	7.38 (7.32, 7.43)	7.38 (7.31, 7.42)	7.38 (7.32, 7.43)	0.990
Po2, M (Q_1, Q_3)	91.50 (53.00, 153.45)	93.50 (55.00, 147.90)	86.60 (52.00, 157.75)	0.910
Glucose, M (Q_1, Q_3)	165.50 (128.00, 226.00)	164.50 (123.00, 212.75)	167.50 (134.00, 240.75)	0.120
Tnt, M (Q_1, Q_3)	0.66 (0.18, 1.56)	0.65 (0.17, 1.64)	0.68 (0.19, 1.52)	0.809
Ferritin, M (Q_1, Q_3)	322.00 (136.50, 858.00)	241.50 (108.25, 597.50)	426.00 (198.75, 1138.50)	<.001
Iron, M (Q_1, Q_3)	37.00 (20.00, 70.25)	36.00 (19.00, 68.50)	37.00 (22.25, 75.50)	0.521
Transferrin, M (Q_1, Q_3)	174.50 (132.75, 219.25)	183.00 (150.25, 227.50)	166.50 (116.50, 212.75)	<.001
Tibc, M (Q_1, Q_3)	227.00 (172.75, 285.25)	238.00 (195.25, 295.50)	216.50 (151.50, 276.75)	<.001
Tsat, M (Q_1, Q_3)	15.94 (9.35, 33.73)	15.09 (8.28, 26.92)	17.47 (9.72, 42.64)	0.017
Gender, n(%)				0.820
F	152 (36.54)	80 (36.04)	72 (37.11)	
M	264 (63.46)	142 (63.96)	122 (62.89)	
Hospital Mortality, n(%)				<.001
0	336 (80.77)	222 (100.00)	114 (58.76)	

1	80 (19.23)	0 (0.00)	80 (41.24)	
Mortality 28d, n(%)				<.001
0	335 (80.53)	222 (100.00)	113 (58.25)	
1	81 (19.47)	0 (0.00)	81 (41.75)	
Sirs, n(%)				0.150
1	3 (0.72)	1 (0.45)	2 (1.03)	
2	69 (16.59)	42 (18.92)	27 (13.92)	
3	168 (40.38)	95 (42.79)	73 (37.63)	
4	176 (42.31)	84 (37.84)	92 (47.42)	
Beta Blocker, n(%)				0.218
0	279 (67.07)	143 (64.41)	136 (70.10)	
1	137 (32.93)	79 (35.59)	58 (29.90)	
Loop Diuretic, n(%)				0.885
0	246 (59.13)	132 (59.46)	114 (58.76)	
1	170 (40.87)	90 (40.54)	80 (41.24)	
Acei, n(%)				0.013
0	390 (93.75)	202 (90.99)	188 (96.91)	
1	26 (6.25)	20 (9.01)	6 (3.09)	
Arb, n(%)				0.806
0	410 (98.56)	218 (98.20)	192 (98.97)	
1	6 (1.44)	4 (1.80)	2 (1.03)	
Copd, n(%)				0.134
0	274 (65.87)	139 (62.61)	135 (69.59)	
1	142 (34.13)	83 (37.39)	59 (30.41)	
Af, n(%)				0.048
0	261 (62.74)	149 (67.12)	112 (57.73)	
1	155 (37.26)	73 (32.88)	82 (42.27)	
Diabetes, n(%)				0.173
0	210 (50.48)	119 (53.60)	91 (46.91)	
1	206 (49.52)	103 (46.40)	103 (53.09)	
Ckd, n(%)				0.213
0	213 (51.20)	120 (54.05)	93 (47.94)	
1	203 (48.80)	102 (45.95)	101 (52.06)	

Table 2

ferritin						
Variables	Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Continuous	1.00(1.00 ~ 1.00)	0.656	1.00(1.00 ~ 1.00)	0.439	1.00(1.00 ~ 1.00)	0.208
Quartile						
T1	Ref.		Ref.		Ref.	
T2	1.72(1.18 ~ 2.52)	0.005	1.80(1.23 ~ 2.64)	0.003	1.54(1.03 ~ 2.30)	0.036
T3	2.48(1.72 ~ 3.59)	<.001	2.76(1.90 ~ 4.00)	<.001	1.88(1.23 ~ 2.87)	0.004
transferrin						
Variables	Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Continuous	0.99(0.99 ~ 0.99)	<.001	0.99(0.99 ~ 0.99)	<.001	0.99(0.99 ~ 0.99)	0.007
Quartile						
T1	Ref.		Ref.		Ref.	
T2	0.54(0.38 ~ 0.75)	<.001	0.52(0.37 ~ 0.73)	<.001	0.64(0.45 ~ 0.91)	0.013
T3	0.48(0.34 ~ 0.68)	<.001	0.47(0.33 ~ 0.67)	<.001	0.68(0.46 ~ 1.02)	0.062
tsat						
Variables	Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Continuous	1.01(1.01 ~ 1.01)	<.001	1.01(1.01 ~ 1.01)	<.001	1.00(1.00 ~ 1.01)	0.191
Quartile						
T1	Ref.		Ref.		Ref.	
T2	1.24(0.87 ~ 1.78)	0.234	1.30(0.90 ~ 1.86)	0.159	1.61(1.11 ~ 2.34)	0.012
T3	1.59(1.11 ~ 2.26)	0.011	1.69(1.19 ~ 2.42)	0.004	1.60(1.10 ~ 2.34)	0.014

Model 1: UnadjustedModel 2: Adjusted for sex, age, and BMI.Model 3: Further adjusted for all variables in Model 2 plus those with $p < 0.05$ in the baseline characteristics (SBP, SAPSII, SOFA, APSIII, RBC, WBC, Hemoglobin, Scr, BUN, ACEI, AF).

Table 3

ferritin						
Variables	Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Quartile						
Q1	Ref.		Ref.		Ref.	
Q2	2.26(1.63 ~ 3.13)	<.001	2.54(1.82 ~ 3.54)	<.001	2.02(1.41 ~ 2.91)	<.001
transferrin						
Variables	Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Quartile						
Q1	Ref.		Ref.		Ref.	
Q2	0.41(0.30 ~ 0.55)	<.001	0.39(0.29 ~ 0.52)	<.001	0.51(0.37 ~ 0.71)	<.001
tsat						
Variables	Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Quartile						
Q1	Ref.		Ref.		Ref.	
Q2	2.00(1.46 ~ 2.75)	<.001	2.10(1.53 ~ 2.89)	<.001	1.66(1.16 ~ 2.36)	0.005

Model 1: UnadjustedModel 2: Adjusted for sex, age, and BMI.Model 3: Further adjusted for all variables in Model 2 plus those with p < 0.05 in the baseline characteristics (SBP, SAPSII, SOFA, APSIII, RBC, WBC, Hemoglobin, Scr, BUN, ACEI, AF).

Table 4

Ferritin

Variable	Subgroup	Patients (n, %)	Group 1 (Events/Total)	Group 2 (Events/Total)	HR (95% CI)	P-value	P for interaction
All patients		416 (100.00)	48 / 153	146 / 263	2.26 (1.63 - 3.13)	<.001	--
Gender	Female (F)	152 (36.54)	22 / 70	50 / 82	2.58 (1.56 - 4.26)	<.001	0.58
	Male (M)	264 (63.46)	26 / 83	96 / 181	2.13 (1.38 - 3.28)	<.001	
COPD	No (0)	274 (65.87)	28 / 97	107 / 177	2.90 (1.91 - 4.40)	<.001	0.042
	Yes (1)	142 (34.13)	20 / 56	39 / 86	1.41 (0.82 - 2.43)	0.208	
Atrial Fibrillation (Af)	No (0)	261 (62.74)	22 / 94	90 / 167	3.02 (1.89 - 4.81)	<.001	0.010
	Yes (1)	155 (37.26)	26 / 59	56 / 96	1.61 (1.01 - 2.56)	0.046	
Diabetes	No (0)	210 (50.48)	19 / 80	72 / 130	3.00 (1.81 - 4.97)	<.001	0.046
	Yes (1)	206 (49.52)	29 / 73	74 / 133	1.77 (1.15 - 2.71)	0.010	
Chronic Kidney Disease (Ckd)	No (0)	213 (51.20)	22 / 84	71 / 129	2.75 (1.71 - 4.45)	<.001	0.098
	Yes (1)	203 (48.80)	26 / 69	75 / 134	1.82 (1.17 - 2.85)	0.008	
Age (Median Split)	Younger Group (1)	208 (50.00)	16 / 69	65 / 139	2.47 (1.43 - 4.28)	0.001	0.857
	Older Group (2)	208 (50.00)	32 / 84	81 / 124	2.34 (1.55 - 3.53)	<.001	

Transferrin

Variable	Subgroup	Patients (n, %)	Group 1 (Events/Total)	Group 2 (Events/Total)	HR (95% CI)	P-value	P for interaction
All patients		416 (100.00)	71 / 103	123 / 313	0.41(0.30 - 0.55)	<.001	--
Gender	Female (F)	152 (36.54)	22 / 30	50 / 122	0.40 (0.24 - 0.66)	<.001	0.964
	Male (M)	264 (63.46)	49 / 73	73 / 191	0.41 (0.28 - 0.59)	<.001	
COPD	No (0)	274 (65.87)	52 / 71	83 / 203	0.38 (0.27 - 0.54)	<.001	0.563
	Yes (1)	142 (34.13)	19 / 32	40 / 110	0.48 (0.28 - 0.83)	0.008	

Atrial Fibrillation (Af)	No (0)	261 (62.74)	44 / 65	68 / 196	0.37 (0.25 - 0.54)	<.001	0.325
	Yes (1)	155 (37.26)	27 / 38	55 / 117	0.47 (0.29 - 0.74)	0.001	
Diabetes	No (0)	210 (50.48)	37 / 50	54 / 160	0.28 (0.19 - 0.43)	<.001	0.012
	Yes (1)	206 (49.52)	34 / 53	69 / 153	0.58 (0.38 - 0.87)	0.009	
Chronic Kidney Disease (Ckd)	No (0)	213 (51.20)	33 / 47	60 / 166	0.32 (0.21 - 0.50)	<.001	0.084
	Yes (1)	203 (48.80)	38 / 56	63 / 147	0.51 (0.34 - 0.77)	0.001	
Age (Median Split)	Younger Group (1)	208 (50.00)	28 / 48	53 / 160	0.43 (0.27 - 0.68)	<.001	0.778
	Older Group (2)	208 (50.00)	43 / 55	70 / 153	0.39 (0.27 - 0.58)	<.001	

TSAT

Variable	Subgroup	Patients (n, %)	Group 1 (Events/Total)	Group 2 (Events/Total)	HR (95% CI)	P-value	P for interaction
All patients		416 (100.00)	141 / 333	53 / 83	1.96 (1.42 - 2.68)	<.001	--
Gender	Female (F)	152 (36.54)	53 / 122	19 / 30	2.00 (1.18 - 3.37)	0.01	0.898
	Male (M)	264 (63.46)	88 / 211	34 / 53	1.93 (1.30 - 2.87)	0.001	
COPD	No (0)	274 (65.87)	97 / 220	38 / 54	2.25 (1.55 - 3.28)	<.001	0.249
	Yes (1)	142 (34.13)	44 / 113	15 / 29	1.49 (0.83 - 2.68)	0.181	
Atrial Fibrillation (Af)	No (0)	261 (62.74)	78 / 205	34 / 56	2.09 (1.40 - 3.13)	<.001	0.566
	Yes (1)	155 (37.26)	63 / 128	19 / 27	1.81 (1.08 - 3.02)	0.024	
Diabetes	No (0)	210 (50.48)	61 / 166	30 / 44	2.57 (1.66 - 3.99)	<.001	0.069
	Yes (1)	206 (49.52)	80 / 167	23 / 39	1.46 (0.92 - 2.32)	0.109	
Chronic Kidney Disease (Ckd)	No (0)	213 (51.20)	63 / 169	30 / 44	2.71 (1.75 - 4.20)	<.001	0.027

	Yes (1)	203 (48.80)	78 / 164	23 / 39	1.37 (0.86 - 2.18)	0.185	
Age (Median Split)	Younger Group (1)	208 (50.00)	56 / 164	25 / 44	2.11 (1.32 - 3.39)	0.002	0.741
	Older Group (2)	208 (50.00)	85 / 169	28 / 39	1.92 (1.25 - 2.95)	0.003	

Figures

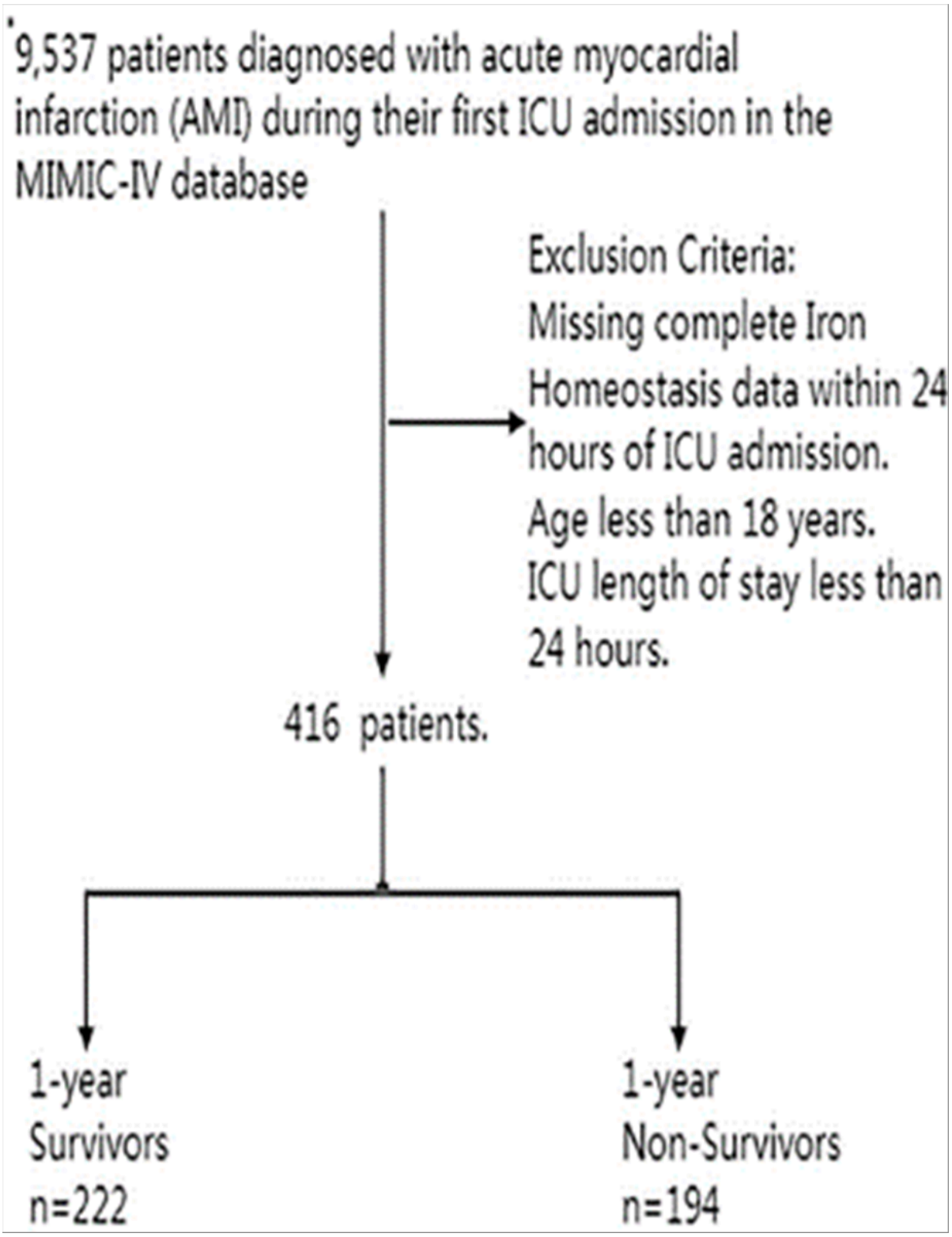


Figure 1

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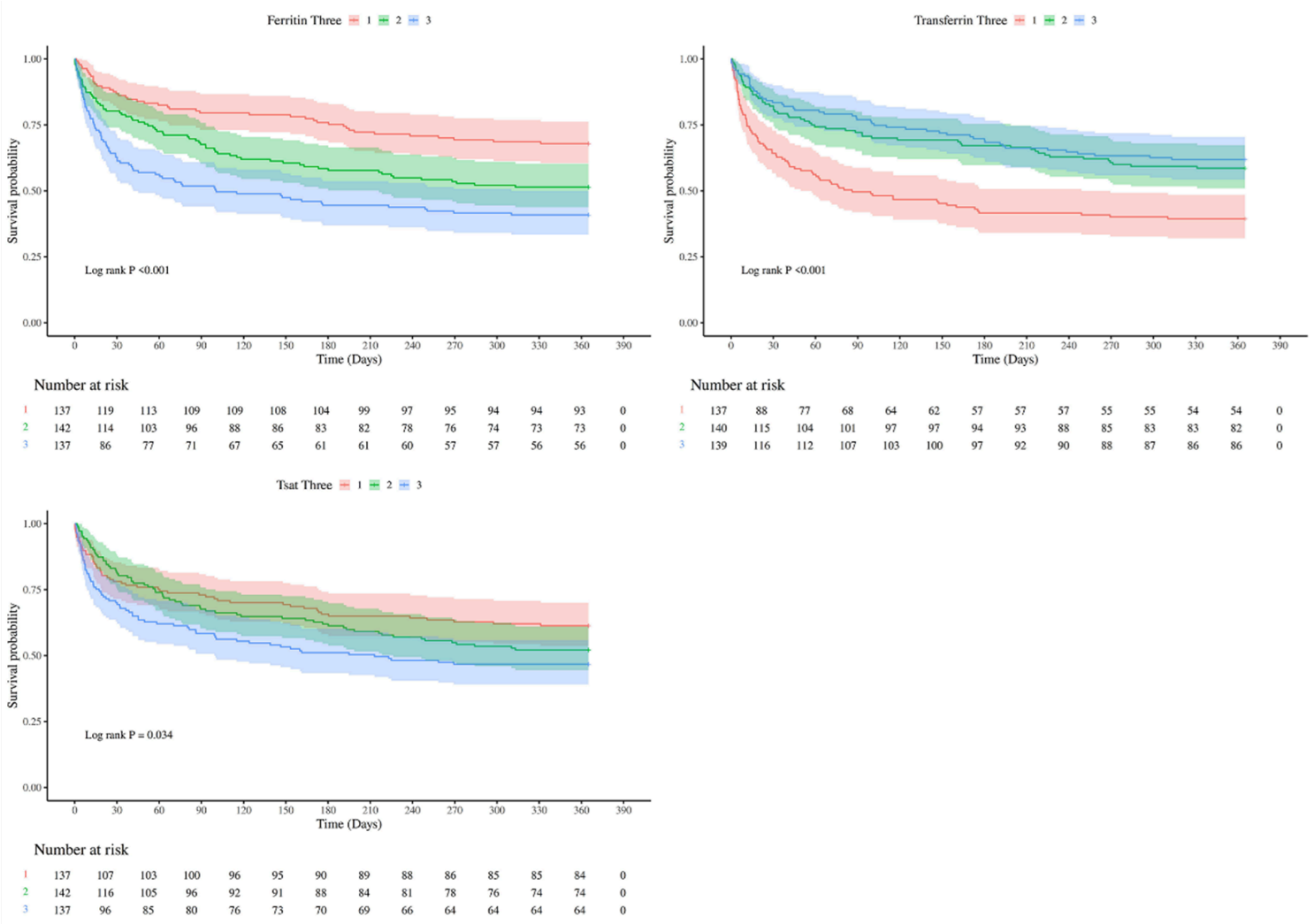


Figure 2

Survival analysis curves for 1-year mortality in patients with acute myocardial infarction: 1. Ferritin 2. Transferrin 3. Total Iron-Binding Capacity (TIBC)

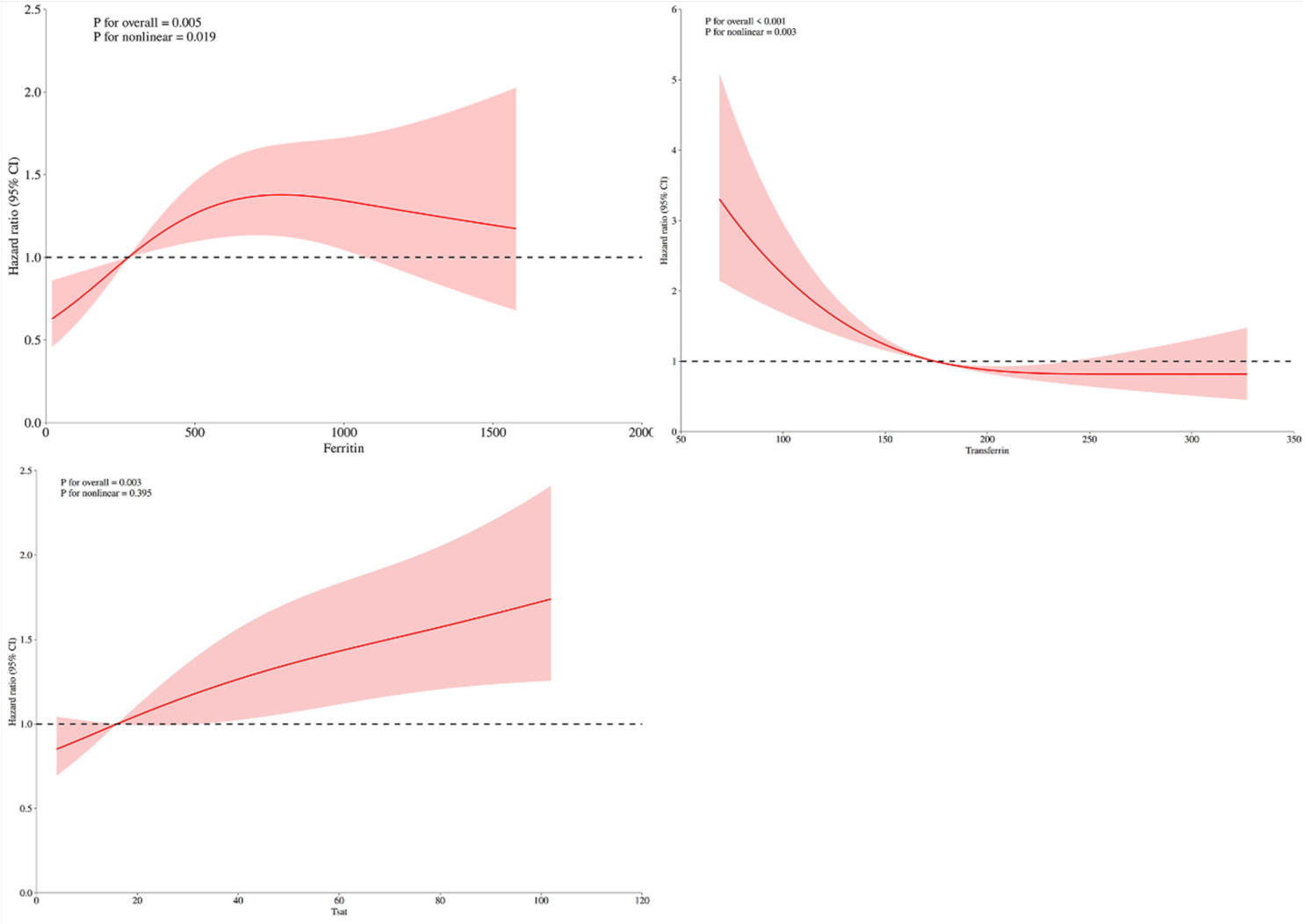
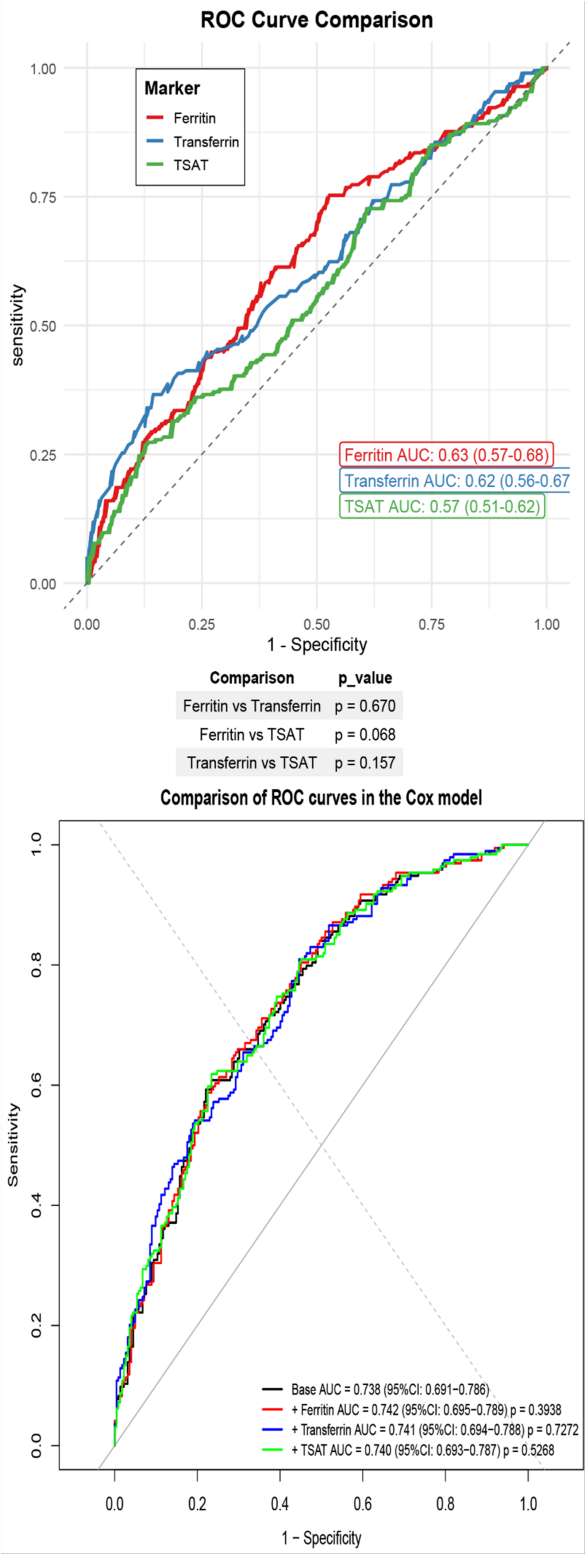


Figure 3

Restricted cubic spline regression analysis of: 1. Ferritin 2. Transferrin 3. Transferrin Saturation



Comparison	p_value
Ferritin vs Transferrin	p = 0.670
Ferritin vs TSAT	p = 0.068
Transferrin vs TSAT	p = 0.157

Figure 4

1: Comparison of ferritin, transferrin, and transferrin saturation in predicting 1-year mortality.

2: Comparison between the base risk model and the base risk model with the addition of ferritin/transferrin/transferrin saturation.

The base risk model includes: age, SBP, SAPSII, SOFA, APSIII, RBC, WBC, hemoglobin, SCr, BUN, ACEI, AF.

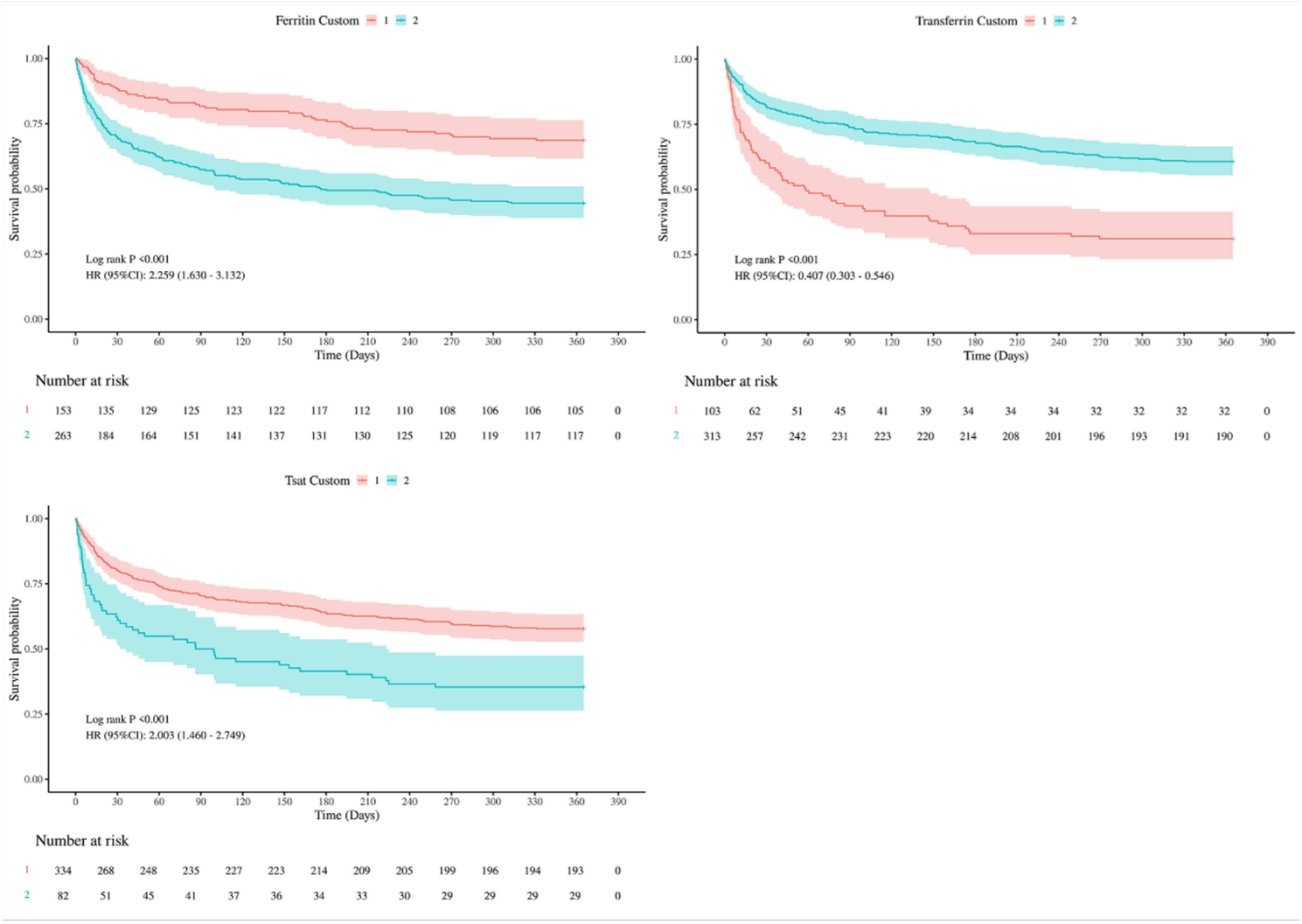


Figure 5

Legend not included with this version.