Association between blood chloride levels and 30-day mortality in patients admitted to the intensive care unit after coronary artery bypass grafting: analysis of data from MIMIC-IV database

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Article

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Abstract

Background: Patients admitted to the intensive care unit (ICU) following coronary artery bypass grafting (CABG) often experience abnormal levels of blood chloride. This study primarily aims to evaluate the association between blood-Cl^--levels and the likelihood of 30-day mortality in this cohort. The authors hypothesized that abnormal blood-Cl^--levels would increase 30-day mortality in these patients.

Methods: The dataset for this research consists of patients who were over the age of 18 and underwent CABG procedures at two renowned establishments in the United States. These institutions are Beth Israel Deaconess Medical Center/Harvard Medical School, located in Boston, and Massachusetts Institute of Technology, situated in Cambridge. The data used in this retrospective cohort study spanned from 2008 to 2019 and were derived from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. Based on the tertiles of blood-Cl^--levels, the participants were divided into Q1, Q2, and Q3 groups. To investigate the association between blood-Cl^--levels and 30-day mortality, several statistical models were used, including a generalized additive model (GAM), restricted cubic spines (RCS), and a two-piecewise linear regression model. The 30-day mortality rates of the three groups were depicted using Kaplan–Meier (K–M) curves. Additionally, we employed multivariable logistic regression models to account for any potential known confounding factors.

Results: Finally, in total, 5224 patients (mean age, 68.8 years; 77% male; 65.9% > 65 years of age) entered the analysis. The rates of 30-day mortality in Q1, Q2, and Q3 groups were 2.8%, 0.9%, and 1.0%, respectively ($p < 0.001$). After adjusting for all latent known covariates, patients in the lower tertile exhibited an increased 30-day mortality risk (adjusted odds ratio [OR] 2.75 [95% confidence interval (CI) 1.32–5.73]; $p = 0.017$). The study concluded a nonlinear association between blood-Cl^--level and 30-day mortality, with a threshold at approximately 107.0 mmol/L. The effect sizes and their corresponding confidence intervals (CIs) below and above the threshold were as follows: 0.77 (0.67–0.87) and 1.15 (0.83–1.6), respectively.

Conclusion: A nonlinear correlation was observed between the blood-Cl^--levels and the mortality rate within 30 days among patients admitted to the ICU following CABG procedures. Elevated and reduced blood-Cl^--levels were linked to higher rates of 30-day mortality, particularly when Cl^- fell below the threshold of 107.0 mmol/L.

Key Points Summary

Question: Is there a correlation between blood chloride (Cl^-) levels and 30-day mortality in patients admitted to the intensive care unit (ICU) after coronary artery bypass grafting (CABG) procedures?

Findings: The findings revealed a U-shaped relationship between blood chloride levels and 30-day mortality.

Meaning: Results of this study may have implications for the clinical management of electrolyte levels in patients admitted to the ICU after CABG surgery.

Introduction

Blood chloride (Cl^-) is the dominant anionic species found in serum electrolytes and is primarily obtained from oral intake. Being the primary extracellular anion, Cl^- constitutes around 33% of the plasma tonicity and contributes to 67% of the total negative charges [1]. Cl^- performs multiple functions in the human body, including regulating body fluids, acid-base and electrolyte balance, preserving electrical neutrality, maintaining osmotic pressure, and muscular activity, which are essential for assessing many pathological conditions [2].

Cl^- plays different roles depending on the study cohort. McCallum et al. concluded a negative correlation between blood-Cl^--levels and the all-cause mortality risk in hypertensive populations [3]. Shaw et al. found that a lower Cl^--load was linked to reduced in-hospital mortality during fluid resuscitation in a cohort with systemic inflammatory response syndrome [4]. Among a group of 1935 critically ill children, an increase in blood-Cl^--level was identified as an ordinary and independent mortality risk variable [5]. In the study conducted by Ji Y et al., a connection was established between the level of Cl^- in the blood and mortality rates in critically ill cirrhotic patients within the ICU [6]. This finding suggests an independent association between blood-Cl^--levels and ICU mortality in this patient population. In a retrospective study involving multiple centers, Zhou L et al. found that patients undergoing continuous ambulatory peritoneal dialysis were at a heightened risk of all-cause mortality [7]. Hence, the results of these studies demonstrate variability depending on the cohorts.

Coronary artery disease (CAD) is a highly fatal disease affecting developed and developing countries [8]. The CAD population represents a vital segment, given that it is treated with open-heart surgery with a high probability of mortality. CAD caused approximately 7.85 million deaths in the United States in 2005 [9] and over 17 million deaths in 2009 [10]. Hence, it is imperative to investigate the relative risk elements in these individuals with the aim of enhancing their chances of survival. Nevertheless, there exists a dearth of scientific inquiry concerning the correlation between them. The primary objective of this study is to scrutinize the connection between the aforementioned factors. Our hypothesis posits that deviant blood-Cl^--levels could be implicated in an elevated propensity for 30-day mortality in this particular group.

Methods

Study design

This retrospective cohort study was conducted on surgical cases performed from November 2008 to 2019 using the MIMIC-IV database (version 2.0). MIMIC-IV is an available and real-world database that consists of 76,943 ICU cases and provides 30-day follow-ups. This database facilitates comprehensive healthcare exploratory research. Additionally, this extensive database contains a wide range of

information, including laboratory measurements, documented vital signs, medication administration, procedure records, outcome events, and other medical records related to patients admitted to the ICU or emergency department at the two medical centers [11].Database exploration clearance was obtained from author JY (certification ID:11088373). The adherence of this study to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines has been ensured [12].

Participants

Approval for the establishment of the MIMIC-IV database has been granted by the Institutional Review Boards (IRBs) of Massachusetts Institute of Technology (0403000206) and the Beth Israel Deaconess Medical Center (2001-P-001699/14). Due to the anonymized and accessible nature of the data utilized in this investigation, specific informed consent from individuals was not necessary [13, 14]. In this research, adult patients who were admitted to the ICU for the first time post-CABG procedures at Harvard Medical School and MIT, were included. To gather information about the cohort, the diagnosis according to the International Classification of Diseases, Ninth and 10th Revision (ICD-9, ICD-10) was utilized. Exclusion criteria involved individuals with missing data on survival time (<0 days), stage of acute kidney injury (AKI) or ventilation time, ICU stay (<1 day), and incomplete or unavailable vital medical records. Eventually, the final analysis included a total of 5224 patients (**Fig 1**).

Data sources and measurement

The cohort study analyzed relative data derived from the MIMIC-IV database in America. In order to extract data, Navicat Premium software (version 16.0.11) was utilized, employing Structured Query Language. The code for data extraction can be found on GitHub [15]. Vital sign data were collected, and the mean values during the ICU stay were calculated. The following data were extracted: basic demographic information (sex, age, weight, height, marital status, race, and admission type, et al.); comorbidities factors (myocardial infarct [MI], peripheral vascular disease [PVD], cerebrovascular disease [CD], mild liver disease [MLD] congestive heart failure [CHD], chronic pulmonary disease [CPD], diabetes with chronic complications [DWCC], hypertension, hyperlipidemia, and atrial fibrillation [AA], etc.); vital signs (heart rate [HR], diastolic blood pressure [DBP], respiration rate [RR], etc.); severity of illness (Sequential Organ Failure Assessment (i.e., “SOFA”) score, and Charlson Comorbidity Index); laboratory investigations (hemoglobin, lactate, pH, bicarbonate, sodium, potassium, and chloride etc.); treatment (ventilation use, continuous renal replacement therapy, norepinephrine, epinephrine etc.); and calculated survival time. During the initial week in the ICU following the CABG procedure, the criteria for AKI were determined by employing both the Kidney Disease Improving Global Outcomes (KDIGO) criteria for serum creatinine and urine output (UOP) [16].

Variable definition

Blood chloride concentration was presented as millimoles per liter (mmol/L). Body mass index (BMI) was determined by dividing an individual’s weight (in kilograms) by the square of their height (in meters). Calcium (mg/dl) × 0.2495, magnesium (mg/dl) × 0.4114, and glucose × 0.0555 were converted to

standardized units (mmol/L). CABG was defined as a history of MI requiring open-heart surgery. Thirty-day death was calculated by subtracting the ICU admission time from the death time as the primary outcome. We defined AKI by using both the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine and urine output (UOP) criteria[16] during the first week in ICU after the CABG procedure.

Potential confounding factors

Significant variables ($P < 0.2$ from the generalized linear model (GLM) and univariable logistic regression models) and those with $P < 0.1$ in the final multivariable logistic regression models [17-19]. The selection details of potential confounding factors are summarized in ***Supplementary File 1***. Six models (1, 2, 3, 4, 5, and 6 [***Table 2***]) were explored sequentially, including covariates to adjust for relative confounders. These factors included patients' demographic variables (age, sex) and comorbidity variables (MI, PVD, CD, and MLD). The analyses were further adjusted for admission type. Finally, analyses were adjusted for sodium, glucose, lactate, bicarbonate, blue light, and norepinephrine use.

Quantitative variables

Serum Cl^- was selected as thequantitativevariable. The cohort was divided into Q1 (90–103.7 mEq/L), Q2 (103.8–106.6 mEq/L), and Q3 (106.7–117.5 mEq/L) groups according to tertiles of blood-Cl^--levels.The Q1 and Q2 groups were the targets of interest, as abnormal blood-Cl^--levels were hypothesized to increase 30-day mortality.

Secondary analysis

The models included all factors chosen from the analysis of univariable logistic regression to control for any potential known confounders. The objective was to evaluate the correlation between levels of blood- Cl^- and mortality within 30 days in this particular cohort. K–M curves were plotted to illustrate differences in 30-day mortality among the three groups (i.e., Q1–Q3). We also examined the association between the fluctuation of blood-Cl^--levels and mortality within 30 days. Subsequently, the regression model was adjusted for the threshold of Cl^- level and the association between each 1mmol/L change in blood-Cl^--levels and 30-day mortality around the threshold was tested.

Exploratory and sensitivity analyses

Additional sensitivity analyses were performed in this study. With exploratory intent, the OR increases for 30-day mortality per 1 mmol/L change in Cl^- were evaluated. The subgroup variables were sex (female, male), age (<65, ≥65 years), MI, PVD, CD, MLD, BMI (< 25, ≥ 25 kg/m^2), and elective surgery.

Statistical analysis

Details regarding the missing variables were summarized in ***Supplementary File 2***. Missing data were handled with multiple imputations using chained equations with three imputed datasets before statistical

analysis. Variables pertaining to continuous data distribution (both normal and nonnormal) and categorical data were presented using various descriptive statistics. The mean with standard deviation (SD), median with interquartile range (IQR), and frequency with percentage (%) were utilized for continuous, nonnormally distributed, and categorical variables, respectively. We tested for statistical differences in percentage, median, and mean among the three groups using the chi-squared ($\chi 2$) test, Kruskal–Wallis test, and one-way analysis of variance (ANOVA), respectively. To investigate the nonlinear correlation between blood chloride levels and mortality within 30 days in ICU patients after CABG procedures, we utilized RCS and GAM techniques.

The K–M survival curve revealed statistical differences in 30-day mortality among the three groups. Potential known factors were introduced in the univariate logistic analyses to investigate the impact of changes in blood-Cl^--levels on 30-day mortality, and then with the included confounders into the multivariate logistic analyses. Six models were applied in the multivariate logistic regression analysis by gradually adding variables to the models, as follows: Model 1 was crude, without any adjustment; sex was added for Model 2; additionally, adjusted age for Model 3; next, MI, PVD, CD, and MLD were introduced to Model 4; then, plus admission type for Model 5; at last, sodium, glucose, lactate, bicarbonate, blood urea nitrogen, and norepinephrine were added to adjust for Model 6. The analysis reference was a Cl^- level of 107.0 mmol/L, and adjustments were made for the aforementioned (model 6) covariates.Furthermore, blood-Cl^--levels were measured at specific percentiles (5th, 35th, 65th, and 95th) and marked with four knots. To assess the correlation between Cl^- and the 30-day mortality, we performed a threshold analysis. This entailed comparing a model containing solely a linear term to a model including both linear and cubic spline terms through a likelihood ratio test. Additionally, we examined the potential influence of confounding factors on the relationship between blood-Cl^--levels and mortality within a 30-day period. Therefore, subgroup analysis with stratified multivariable logistic regression models was conducted, and the interactions between subgroups were examined using likelihood ratio testing.

We introduced unadjusted and adjusted ORs of the logistic regression models to report the results. Two-tailed tests and corresponding 95% CIs were applied for all analyses. $p \leq 0.05$ and $p < .017$ were considered significant differences in the pairwise and multiple comparison analyses. We conducted all analyses utilizing R (http://www.R-project.org, The R Foundation for Statistical Computing, Vienna, Austria) and the Free Statistics software, version 1.8.

Results

Study cohort and characteristics

5952 intensive care unit (ICU) admissions were recorded following coronary artery bypass graft (CABG) procedures. Participants who did not have their first ICU admission (n=321), those with repeat admissions (n=15), ICU stays of less than 1 day (n=295), and individuals with null survival time and other factors (n=97) were excluded. (***Fig 1***) The formal analysis comprised 5224 adult patients admitted to the

ICU after undergoing CABG procedures. The average age and blood chloride levels were 68.8 ± 10.2 years and 105.1 ± 3.7 mmol/L, respectively. Among the study population, 77.0% (n=4023) were males. The patients were categorized into three groups based on tertile of chloride, with 1709, 1728, and 1787 individuals in the lower, middle, and upper groups, respectively. ***Table 1*** provides a summary of the baseline characteristics of the patients.

Thirty-day mortality

During the 30 days following admission to the ICU after CABG procedures, 80 patients (1.5%) experienced mortality. The death distribution across the tertiles was as follows: 2.8% in Q1, 0.9% in Q2, and 1.0% in Q3 (**Table 2**, $p < 0.001$). By employing multivariate logistic regression and RCS analysis, we identified a nonlinear association between blood chloride levels and mortality within the 30-day timeframe (p for nonlinearity < 0.001). The OR increased by 23.0% per 1 mmol/L decrease in Cl^- levels below 107.0 mmol/L and remained stable when Cl^- exceeded this threshold (***Table 3***). After controlling for variables that could potentially affect the results (Model 6), individuals in the Q1 group (< 103.7 mol/L) exhibited an increased risk of mortality within 30 days (adjusted OR 2.75 [95% CI 1.32–5.73]) compared to those in the Q2 group. Additionally, the Q3 group (≥ 106.8 mmol/L) displayed a slightly elevated risk (adjusted OR 1.08 [95% CI 0.47–2.48] (p for trend = .017).

Effects of serum Cl^- on 30-day mortality

The threshold of the blood-Cl^--level was determined to be 107.0 mmol/L (***Table 3***) using a two-piecewise Cox regression model. Within this threshold, the OR increased by 23.0% per 1 mmol/L decrease in Cl^-, while it increased proportionally when the blood-Cl^--level exceeded this threshold. The 30-day mortality rate in the Q1 group showed a significant difference compared to Q2 and Q3 (***Fig 2a***) based on the K–M curves ($p < .0001$ [with Q2 as the reference]).

Exploratory and sensitivity analyses

In order to examine the correlation between blood chloride concentration and mortality within 30 days, this study conducted subgroup analyses. These analyses consistently demonstrated a robust and dependable association (***Fig 3***) among different subgroups, encompassing gender (female, male), age (<65, ≥65 years), MI, PVD, MLD, BMI (< 25, ≥ 25 kg/m2), and elective surgery. Significantly, no evident interactions were observed among the subgroups analyzed. The length of ventilation, length of stay (LOS) in hospital and ICU were longest in the Q1 group ($p<0.001$, ***Supplementary File 3***).

Discussion

This retrospective cohort study examined the correlation between the average blood chloride level and mortality rate within 30 days among elderly individuals admitted to the ICU following CABG procedures.

The findings of the study revealed a 1.5% or 30-day mortality rate. An independent correlation was found between blood-Cl^--levels and mortality within 30 days in the lower and upper tertiles of Cl^- in post-CABG patients admitted to the ICU, especially when the blood-Cl^--level was less than 107.0 mmol/L.

In line with prior investigations, we observed a notable fatality rate among individuals categorized in the Q1 group, implying a robust association between diminished Cl^- levels and heightened risk of mortality in patients enduring SIRS [3] along with critically ill individuals afflicted with acute kidney injury [20]. After accounting for potential variables, McCallum et al. discovered an observed increase in the hazard ratio for all-cause mortality by 1.5% when the blood chloride concentration decreased by 1 mmol/L [3]. Our study revealed an inflection point at a blood-Cl^--level of approximately 107.0 mmol/L. The OR increased by 23.0% per 1 mmol/L decrease within this threshold and remained insignificantly changed when blood-Cl^- exceeded this level. After adjusting for confounding factors (model 6), the risk for 30-day mortality was also more significant in the lower tertile (< 103.7 mol/L; adjusted OR 2.72 [95% CI 1.37–5.4]) and upper tertile (≥ 106.8 mmol/L; adjusted OR 1.32 [95% CI 0.61–2.88]; *p* for trend = 0.017) than in the middle tertile. These findings contribute to mounting observational evidence supporting the potential consequences of severe clinical adjustment of blood-Cl^--levels in ICU patients after CABG procedures.

Most previous studies have explored the relationship between blood-Cl^--levels and mortality rates occurance between pediatric and adult populations, respectively [5, 21–25]. Related research has since been conducted. Professor McCallum et al. encouraged studies investigating the association between blood-Cl^--levels and outcomes in the Japanese population in 2014 [26]. In pediatrics, researchers have mainly focused on children diagnosed with critical illnesses [5, 23, 27] and septic shock [22]. Among adults, the cohorts were primarily distributed to patients diagnosed with systemic inflammatory response syndrome [4, 28], critically ill patients with [6] or without cirrhosis [27], heart failure [29, 30], hypertension [3], and post-noncardiac surgery patients [24, 25]. Limited research has been conducted to investigate the correlation between blood Cl^- and mortality within 30 days in patients who have been admitted to the ICU following CABG procedures. Dirk et al. first reported an association between blood-Cl^--levels and mortality based on the human population in 1998 [31]. The results were based on a large observational cohort and concluded that blood-Cl^--level was one of the most robust and autonomous prognosticators for overall mortality associated with cardiovascular disease.

Shaw et al. found a positive correlation between volume-adjusted chloride and mortality odds when the blood-Cl^--level exceeded 110 mmol/L [4]—suggesting that there may be potential mortality risks associated with Cl^- levels above the upper ranges. In this research, it was discovered that there exists a significant connection between an escalated burden of Cl^- and an augmented rate of mortality during hospitalization. By considering and accounting for various potentially influential covariables, the utilization of multi–logistic regression models and RCS exposed a distinctive curvilinear association (Fig. 2b, p for nonlinearity < 0.001) linking Cl^--load and the likelihood of 30-day mortality. This outcome aligns with the investigation conducted by Fu et al., which concentrated on scrutinizing the Na^+/Cl^-ratio concerning in-hospital mortality in geriatric patients afflicted with heart failure [29].

Previous studies explored the association between Cl^- and AKI and mostly concluded that high level of Cl^- is associated with increased incidences of AKI [5, 21–25]. In this study, we also made somemore analysis to detect this assiociation. It is inconsistent with the distribution of kidney diseases in the three subgroups. For the overall AKI occurance was 17.3%, patients in the Q1, Q2 and Q3 groups combined with renal disease history were 14.6% 25.5% and 15.4% respectively ($p < 0.001$). While the severe AKI occurance in the Q1, Q2, and Q3 groups was 4%, 0.8%, and 0.2%, respectively, and the length of ventilation, length of hospital and ICU stays were longest in the Q1 group ($p < 0.001$, **Supplementary File 3**). This indicates that hypochloremia may be a risk factor for sereve AKI, consistenting with previous researches [5, 21–25]. We also explored a further association between hypochloremia and length of ventilation, LOS in hospital and ICU.

Logistic regression and RCS exposed a distinctive linear association linking serum Cl^- level and the likelihood of AKI at any stage after adjusted for all known confounders (**Supplementary File 4**). And the 30-day mortality rates were the highest in Q1 group. This assiociation still exists and maintains stable after adjusting for potential covariates.

Strengths

There were several strengths to our study. First, the data were high quality, consisting of two medical centers in America, and multiple variables were included, with 5224 cases and 30-day follow-ups. Second, we calculated the mean values of all continuous variables during the ICU stay, which may be much closer to reality and may add strength to the limited studies in the future. Finally, the outcomes may serve as a reference value to clinicians treating similar patients in the future.

Limitations

However, this retrospective cohort study also has a few limitations. As observed in all observational studies, uncontrolled potential confounders may have been present. Our study focused exclusively on examining the correlation between blood-Cl^--level and mortality within 30 days among the cohort admitted to the ICU following open-heart CABG surgery. Whether abnormal blood-Cl^--levels cause the pathological process or whether 30-day mortality is a secondary feature of the causative metabolic derangements is unclear. Cl^- grouping may have introduced some bias; we grouped according to the tertile of blood-Cl^--level rather than the standard grouping method used in previous studies; however, we performed a threshold effect analysis to determine the inflection point at approximately 107.0 mmol/L. It is reasonable for the inflection point to be close to the middle tertile of the subgroup point (106.8 mmol/L). Due to the constraints of the MIMIC-IV database, we could not determine the exact mechanism between blood chloride concentration and mortality within 30 days in this cohort.

Conclusion

In summary, this investigation uncovered a notable link between abnormal levels of chloride in blood and a rise in mortality within the initial 30-day period for individuals admitted to the ICU post-CABG procedures. Because this study was observational, much should be carefully considered in future real-world research. Conclusions can only be generalized to adult patients in America admitted to the ICU after CABG procedures. Future research should focus on conducting randomized controlled trials and basic research to further investigate the differences in outcomes and clarify the relationship within this specific cohort.

Abbreviations

CAD
coronary artery disease
CI
confidence interval
OR
odds ratio
Cl^-
chloride
CABG
coronary artery bypass grafting
ICU
intensive care unit
ICD-9/10
International Classification of Diseases,Ninth/10th Revisions
IQR
interquartile range
K–M
Kaplan–Meier
MIT
Massachusetts Institute of Technology
MIMIC-IV
Medical Information Mart for Intensive Care-IV (MIMIC-IV)
SOFA
Sequential Organ Failure Assessment score
AKI
acute kidney injury
BMI
body mass index
RCS
restricted cubic spline

CHF
congestive heart failure
MI
myocardial infarct
PVD
peripheral vascular disease
CVD
cerebrovascular disease
CPD
chronic pulmonary disease
RD
rheumatic disease
MLD
mild liver disease
DWC
diabetes with chronic complication
AF
atrial fibrillation
CCI
charlson comorbidity index
HR
heart rate
T
temperature
MBP
mean arterial pressure
Hb
hemoglobin
RR
respiration rate
LOS
length of hospital stay.

Declarations

Consent for publication

All the authors read and approved the final manuscript and decided to submit and publish the manuscript.

Availability of data and materials

The extraction code for the datasets are available on GitHub, *http://github.com/MIT-LCP/mimic-code*).

Competing interests

None.

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Authors' contributions

J.M.Y and L.Z: conceived the study design and data extraction, conducted the literature review and data analysis, drafted the manuscript, and interpreted and critically revised the manuscript. They contributed equally to the manuscript. H.Q.L. and J.J.Y: the corresponding authors who contributed to draft and critically revise the manuscript, contributed equally to this work.

All the authors gave their final approval, agreed to submit and publish the manuscript, and declared no conflicts of interest.

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Tables

Tables 1 to 3 are available in the Supplementary Files section

Figures

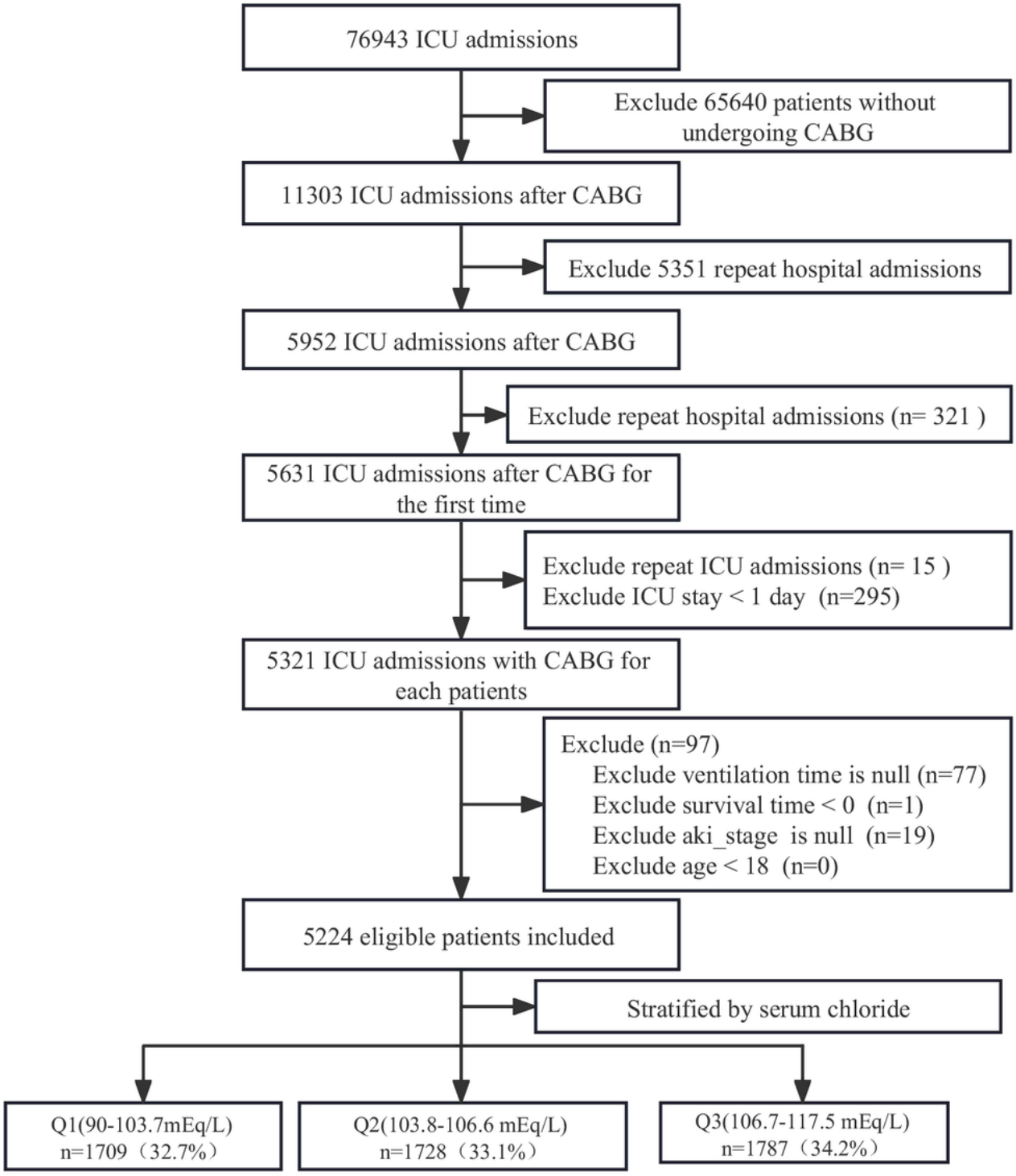

Figure 1

Flowchart of the study cohort

Note: ICU, Intensive Care Unit; CABG, Coronary Artery Bypass Grafting, AKI-stage, the stage of Acute Kidney Injury.

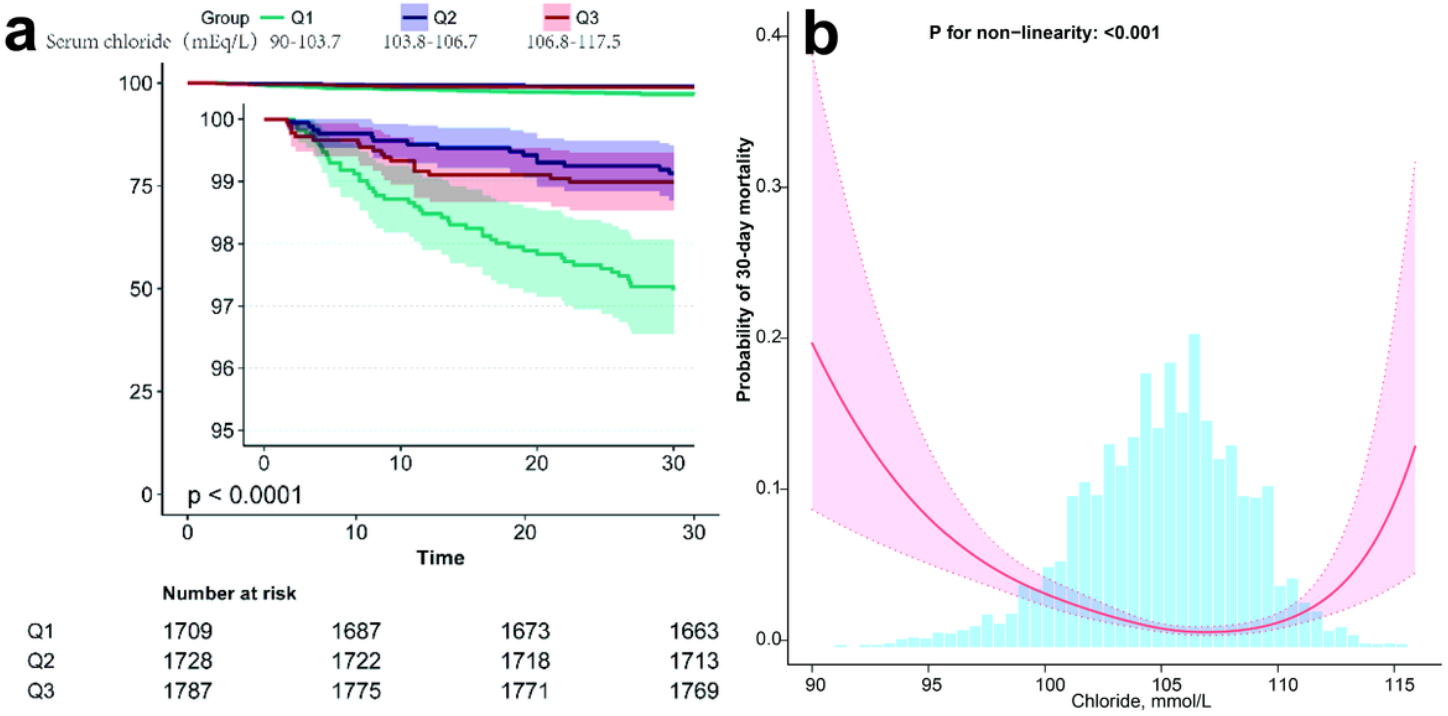

Figure 2

Kaplan-Meier survival curves and Multivariable logistic regression to display the association between Cl^- and 30-day mortality.

a. Kaplan-Meier survival curves for 30-day mortality in patients admitted to ICU after CABG grouped by three quartiles of serum Cl^-. The colors of the quintiles correspond to the colors depicted above. The Q1 group had the worst 30-day survival, which declined with declining of Cl^- (log-rank test: $P < 0.0001$).

b. Multivariable logistic regression displayed a nonlinear association between Cl^- and 30-day mortality (only 99.9% of the data was used). Cl^- was entered as a continuous variable. The red line and pink shaded area represent the estimated values and 95% confidence intervals.

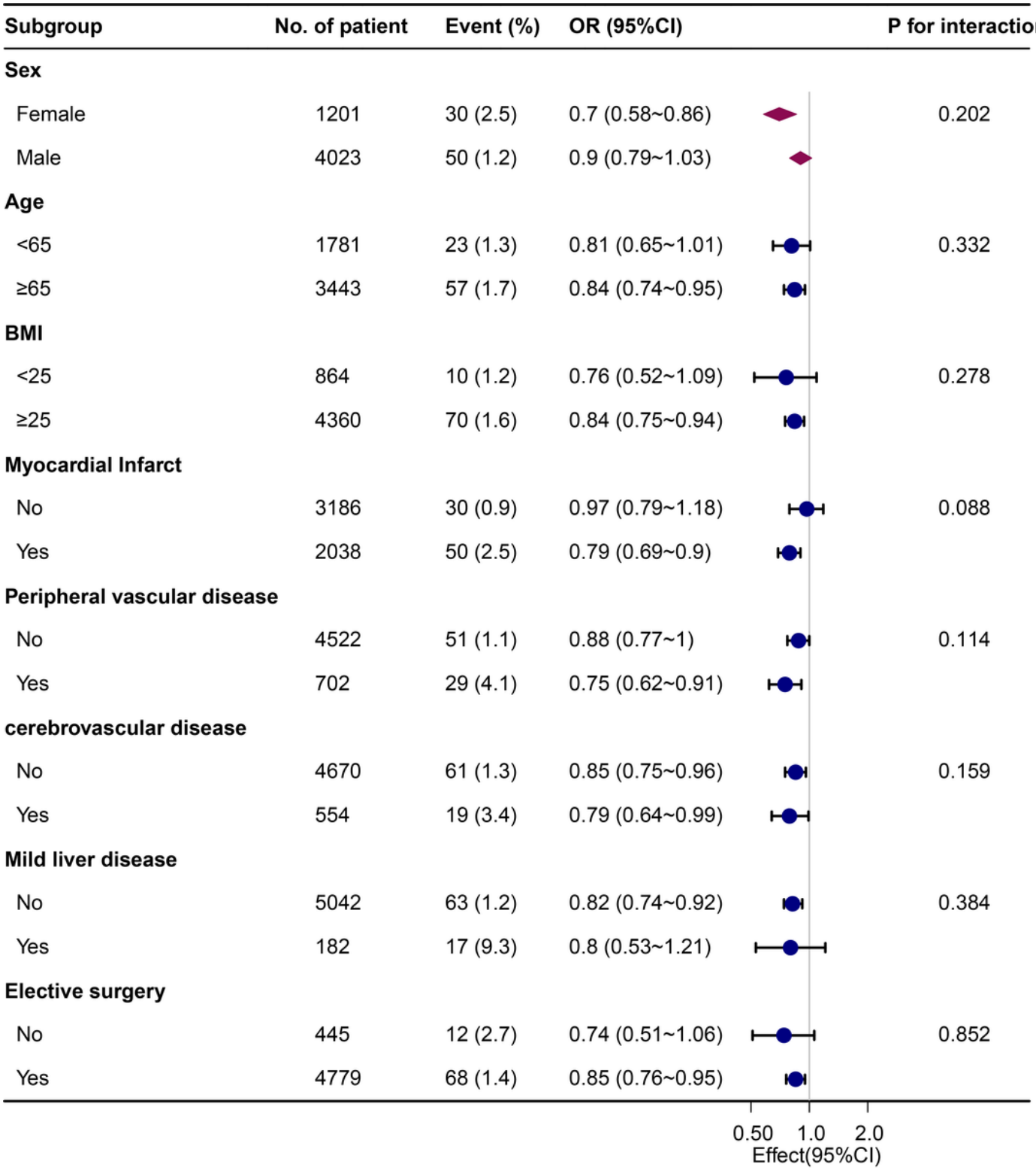

Figure 3

Subgroup analysis displayed by Forest plot shows ORs of 30-day mortality. OR: Odds Ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile1.docx
- SupplementaryFile2.docx
- SupplementaryFile3.docx
- SupplementaryFile4.docx
- table1.docx
- table2.docx
- table3.docx