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Time series analysis Between Serum Calcium Levels and 60-Day Mortality in Critically ill Patients with Multiple Myeloma: A Retrospective Cohort Study

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Research Article

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Abstract

Background

Hypercalcemia is a well-recognized adverse prognostic factor in patients with multiple myeloma (MM), particularly in critically ill subgroups where its incidence is substantially higher than in the general MM population. However, the prognostic value of dynamic serum calcium fluctuations during intensive care unit (ICU) hospitalization remains underexplored, limiting the ability to refine risk stratification and personalized management.

Objective

This study aims to identify heterogeneous serum calcium trajectories in critically ill MM patients and investigate their association with 60-day mortality.

Methods

A retrospective cohort study was conducted using data from 254 critically ill MM patients extracted from the MIMIC-IV database. Latent Class Growth Modeling (LCGM) was applied to classify serum calcium trajectories over the first 28 days of hospitalization, with measurements collected at predefined time points-. Multivariable Cox proportional hazards regression models (adjusted for demographic, clinical, and disease severity covariates) and Kaplan-Meier (K-M) curves were used to assess the association between trajectory patterns and 60-day mortality. Sensitivity analyses included trajectory reclassification and E-value assessment to validate result robustness.

Results

Four distinct serum calcium trajectories were identified: low-level (n = 90, 35.43%), medium-level (n = 138, 57.48%), U-shaped (n = 9, 3.54%), and high-level (n = 17, 6.68%). Compared with the high-level trajectory (reference group), the low-level (HR = 0.17; 95% CI 0.07–0.41; P < 0.001) and medium-level (HR = 0.26; 95% CI 0.12–0.56; P = 0.001) trajectories were independently associated with significantly lower 60-day mortality. The U-shaped trajectory showed no significant mortality difference from the high-level trajectory (HR = 0.56; 95% CI 0.14–2.25; P = 0.416). K-M analysis confirmed the prognostic gradient across trajectories, and sensitivity analysis (E-value = 2.49) validated the robustness of these associations to unmeasured confounding.

Conclusion

Persistently high or rebound (U-shaped) serum calcium trajectories are independent predictors of increased 60-day mortality in critically ill MM patients, reflecting underlying aggressive disease biology or treatment resistance. Dynamic serum calcium monitoring via trajectory analysis refines early risk stratification and provides actionable insights for guiding personalized ICU management, addressing an unmet need in current clinical practice.

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells within the bone marrow. Globally, MM incidence is on the rise, making it the second most common hematologic cancer after Hodgkin's lymphoma. In Europe, the annual incidence rate ranges from 4.5 to 6.0 cases per 100,000 individuals, with a corresponding mortality rate of 4.1 per 100,000 [1]. Complications associated with MM include anemia, hypercalcemia, renal dysfunction, and bone disease. Hypercalcemia is observed in 19.5% of MM patients at diagnosis, with severity ranging from mild to life-threatening, and is frequently linked to bone lesions, kidney dysfunction, and high-risk chromosomal abnormalities in MM [2, 3]. Notably, emerging evidence suggests that critically ill MM patients admitted to the intensive care unit (ICU) exhibit a significantly higher incidence of hypercalcemia (up to 30%-40%) compared to the general MM population. In such patients, hypercalcemia is not only a consequence of bone resorption driven by myeloma cell-derived cytokines, but also intertwined with ICU-specific insults such as acute kidney injury (AKI) and sepsis, forming a vicious cycle that accelerates organ dysfunction and poor outcomes. This unique pathophysiological feature highlights the need to explore dynamic calcium changes rather than static baseline values in this population[4]. Hypercalcemia at initial diagnosis of MM is widely recognized as an adverse prognostic factor [2, 3]. Given the complexity of critical illness and the variability of medical interventions (e.g., anti-myeloma therapy that may alter bone metabolism, renal replacement therapy that regulates calcium excretion), serum calcium levels change dynamically over time. The persistence or exacerbation of hypercalcemia in critically ill MM patients may further increase mortality risk.

Guidelines, including the EHA-ESMO clinical practice guidelines for MM, recommend monthly or at least quarterly monitoring of core laboratory parameters (complete blood count, creatinine, and serum calcium) during follow-up, but lack guidance on interpreting dynamic fluctuations, leaving clinicians unable to leverage serial calcium data for real-time risk assessment in ICU settings[5, 6]. A recent study further demonstrated a nonlinear relationship between serum calcium levels and in-hospital mortality in critically ill MM patients, with a serum calcium level of approximately 8.40 mg/dL associated with the lowest mortality risk and risk increasing with rising levels, an important consideration for ICU clinicians[6]. Despite this, most current studies focus on baseline serum calcium data from newly diagnosed MM patients at admission [2, 6], failing to account for the dynamic fluctuations of serum calcium levels during ICU stay. Given the complexity of critical illness and the variability of medical interventions, serum calcium levels change dynamically over time, and investigating these time-series changes and their prognostic implications is crucial for optimizing risk stratification and treatment adjustment [7].

Medical time series analysis (TSA) has been widely applied in prognostic studies [8]. Among TSA methods, the Latent Class Growth Modeling (LCGM) is particularly valuable for identifying heterogeneous trajectory subgroups in heterogeneous populations such as critically ill MM patients who may exhibit diverse calcium change patterns, by partitioning the population into latent classes based on individual characteristics (e.g., intercepts and slopes) and modeling class-specific change patterns over time[9]. Trajectory analysis using LCGM has been successfully applied to characterize dynamic biomarkers in various hematologic and critical diseases[10], but to date, no studies have utilized this approach to explore the relationship between dynamic serum calcium trajectories and mortality in MM patients, especially in the high-risk critically ill subgroup.

To address this research gap, the present study leverages data from the MIMIC-IV database to construct LCGM of serum calcium trajectories during the first 28 days of hospitalization, integrating both baseline measurements and dynamic time-series data. The primary objectives are to identify distinct serum calcium trajectories in critically ill MM patients, evaluate their association with 60-day mortality, and provide evidence for refining early risk stratification and guiding personalized clinical decisions.

Materials and Methods

Population and Data Collection

This retrospective cohort study utilized the Medical Information Mart for Intensive Care-IV (MIMIC-IV v3.0) database, comprising de-identified clinical data from >70,000 intensive care unit (ICU) admissions at Beth Israel Deaconess Medical Center (Boston, MA) between 2008 and 2019[6]. Access to the MIMIC-IV database was obtained in accordance with the official access protocol specified by PhysioNet (https://physionet.org/content/mimiciv/3.0/). Access to the database required completion of the "CITI Data or Specimens Only Research" training course on the National Institutes of Health (NIH) website, with approval granted for data extraction for research purposes (Certificate No for Zhang: ID: 13813672). Ethical oversight was provided by institutional review boards of Massachusetts Institute Technology and Beth Israel Deaconess Medical Center. Informed consent was waived given the retrospective, de-identified nature of the data[6].

Structured Query Language (SQL), PostgreSQL (version 13.0), and Navicat software (version 16.0) were used to identify the cohort and extract relevant clinical data [11]. Inclusion criteria were defined as: (1) adult patients aged ≥18 years; (2) a confirmed diagnosis of MM based on International Classification of Diseases (ICD) coding: ICD-9 codes (203.00, 203.01, 203.02) or ICD-10 codes (C90.00, C90.01, C90.02) [6]; (3) first-time ICU admission (to avoid duplicate patient data); and (4) availability of at least two serum calcium measurements during hospitalization. Exclusion criteria were: (1) absence of baseline serum calcium measurement on ICU admission; (2) fewer than two serum calcium measurements throughout the ICU hospitalization period; (3) incomplete data on the primary outcome (60-day mortality).

Demographics, comorbidities, and laboratory indicators were extracted from the MIMIC-IV database. Serum calcium levels were systematically collected at predefined time points: ICU days 1, 3, 5, and 7,

with weekly averages calculated for weeks 2, 3, and 4 of hospitalization. Additionally, the minimum, maximum, and mean serum calcium values during the entire ICU stay were computed. For missing serum calcium data on days 3, 5, or 7, a last-observation-carried-forward approach was applied, wherein the nearest adjacent available measurement was imputed. For other laboratory parameters, maximum, minimum, or mean values were selected based on clinical relevance and prior literature[10, 12]. The primary outcome of interest was 60-day mortality. Variables with missing data exceeding 10% were excluded from the analysis, consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline[13]. For remaining variables with minor missingness (<10%), multiple imputation was performed using chained equations with 5 imputed datasets via the mice package in R [14].

Identification of Serum Calcium Trajectory Subgroups and Model Selection

Heterogeneous serum calcium trajectories were identified using the R package "lcmm" (version 2.0.2) via LCGM [7]. A latent class mixed model was applied for longitudinal serum calcium data analysis, and a parametric survival model with a class-specific Weibull distribution was incorporated to characterize the baseline hazard function, enabling simultaneous modeling of longitudinal trajectories and time-to-60-day-mortality outcomes [7].Trajectory modeling was based on serum calcium data systematically collected within the initial 28 days after ICU admission to be consistent with the study's predefined observation window, including measurements on ICU days 1, 3, 5, and 7, as well as weekly averages for weeks 2-4. Both linear and quadratic functional forms for the time variable were evaluated to optimize model fit. Quadratic terms were included to capture potential acceleration or deceleration in serum calcium changes commonly observed in critically ill patients[15].

Model selection was guided by a comprehensive set of criteria to ensure statistical robustness and clinical interpretability:Lower values of the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample-adjusted BIC (SABIC) indicated superior model fit; A significant P-value (< 0.05) from the Lo-Mendell–Rubin (LMR) adjusted likelihood ratio test supported adding an additional trajectory class; Visual inspection of trajectory plots was conducted to confirm the clinical plausibility of identified patterns; Higher maximum log-likelihood and entropy (≥ 0.80, indicating strong classification accuracy) were prioritized; Robust subgroup classification required an average posterior probability ≥ 70% for each class; Only models with each subgroup containing > 3% of the total study population were retained to avoid unstable estimates from small subgroups[10, 16, 17].The optimal number of trajectory subgroups was determined by balancing all aforementioned criteria, with the final model selected based on the best overall fit and clinical interpretability.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) for normally distributed data (assessed via the Shapiro-Wilk test) and median (interquartile range, IQR) for skewed data. Group comparisons across latent trajectory classes were performed using the Kruskal-Wallis test for continuous variables. Categorical variables were presented as counts (percentages, %), with group

comparisons conducted using Pearson's chi-squared test; Fisher's exact test was used when the expected frequency of any cell was < 5. Univariate and multivariate Cox proportional hazards regression analyses were performed to evaluate the association between candidate variables (including serum calcium trajectories) and 60-day mortality. The selection of covariates for adjustment in multivariate models was guided by three principles: (1) clinical relevance based on prior literature[18], (2) expert consensus on risk factors for mortality in critically ill MM patients[6], and (3) statistical significance ($p < 0.05$) in univariate Cox regression. Four hierarchical multivariate Cox models were constructed to assess the robustness of the association between serum calcium trajectories and 60-day mortality. Model 1: Unadjusted (only serum calcium trajectory as the predictor);Model 2: Adjusted for age and gender (basic demographic confounders);Model 3: Adjusted for age, gender, mean systolic blood pressure (SBP_mean), maximum blood urea nitrogen (Bun_max), minimum platelet count (Plt_min), and congestive heart failure (clinical and laboratory confounders);Model 4: Fully adjusted for age, gender, SBP_mean, Bun_max, Plt_min, congestive heart failure, Acute Physiology Score III (APSIII), Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS), and Sequential Organ Failure Assessment (SOFA) score (adding disease severity indices). Kaplan–Meier (KM) survival curves were generated to visualize survival probabilities across serum calcium trajectory classes, with between-group differences evaluated using the log-rank test. The E-value calculation Quantifies the potential impact of unmeasured confounding on the observed associations. The E-value was defined as the minimum strength of association (on the risk ratio scale) that an unmeasured confounder would need to have with both the exposure (serum calcium trajectory) and the outcome (60-day mortality), conditional on measured covariates, to fully explain the observed association [19]. All statistical analyses were conducted using R Statistical Software (version 4.2.2; http://www.R-project.org, The R Foundation) and the Free Statistics Analysis Platform (version 2.1.1; Beijing, China). Specific R packages included survival for Cox regression and KM analysis, and car for testing model assumptions. A two-tailed p-value < 0.05 was considered statistically significant[20].

Results

Baseline characteristics

A total of 254 patients were included in this study after screening according to predefined inclusion and exclusion criteria (Supplementary Figure 1). The overall 60-day mortality rate was 24.02% (61/254). The baseline characteristics of the study population stratified by 60-day mortality status are summarized in Table 1.

Compared with the surviving group (n = 193), the non-surviving group (n = 61) had a significantly older age and a higher prevalence of congestive heart failure. Regarding vital signs, the non-surviving group exhibited a lower mean diastolic blood pressure and a higher mean respiratory rate. For laboratory parameters, the non-surviving group had a significantly lower minimum platelet count and a higher maximum blood urea nitrogen level. In terms of illness severity scores, the non-surviving group had significantly higher scores on the APSIII, SAPSII, OASIS, and SOFA score.

Identification of subpopulations using the LCGM

The optimal number of serum calcium trajectory subgroups was determined based on multiple model fit metrics, including log-likelihood, AIC, BIC, SABIC, entropy, and class composition ratio (Table 2). As the number of classes increased from 1 to 5, the log-likelihood, AIC, and SABIC values initially decreased and then increased, with the 4-class model yielding the lowest AIC (2262.018) and SABIC (2271.196) values. Additionally, the 4-class model exhibited a moderate log-likelihood (-1106.008962), a relatively high entropy (0.683), and each class accounted for >3% of the total population (ranging from 3.544% to 57.480%), meeting the criteria for robust subgroup classification.Thus, the 4-class model was selected as the optimal solution, and the trajectories were labeled as follows (Figure 1). Class 1(Low-level trajectory, 35.433%, n = 90) of patients, characterized by a slight increase from an initially low serum calcium level; Class 2 (Medium-level trajectory, 57.480%, n = 138) of patients, characterized by a slight decrease from a moderate baseline serum calcium level;

Class 3 (U-shaped trajectory, 3.544%, n = 9) of patients, characterized by serum calcium levels decreasing from an initial high level to a low point and then rising back to a medium level; Class 4 (High-level trajectory, 6.683%, n = 17) of patients, characterized by persistently high serum calcium levels maintained throughout the observation period. The baseline characteristics of the study population stratified by serum calcium trajectories are summarized in Supplementary Table 1.

Univariable Cox Regression Analysis

As shown in Table 3, univariable Cox regression analysis was performed with the high-level trajectory (Class 4) as the reference group. The results revealed that patients in the low-level trajectory (Class 1) and medium-level trajectory (Class 2) had significantly lower 60-day mortality risk (Class 1: HR = 0.28, 95% CI = 0.13-0.63, p = 0.002; Class 2: HR = 0.34, 95% CI = 0.16-0.71, p = 0.004). In contrast, no significant difference in 60-day mortality was observed between the U-shaped trajectory (Class 3) and the reference group (HR = 0.51, 95% CI = 0.14-1.89, p = 0.313).Additionally, univariable analysis identified several independent risk factors for 60-day mortality, including older age, lower DBP-mean, higher RR-mean, lower PLT-min, higher BUN-max, presence of congestive heart failure, and higher APSIII, SAPSII, OASIS, and SOFA scores (all $p < 0.001$).

Multivariable Cox Regression Analysis

To adjust for potential confounding factors, four hierarchical multivariable Cox regression models were constructed (Table 4). In the fully adjusted model (Model 4), which included age, gender, SBP-mean, BUN-max, PLT-min, congestive heart failure, APSIII, SAPSII, OASIS, and SOFA score, the associations between serum calcium trajectories and 60-day mortality remained robust. Compared with the high-level trajectory (Class 4), the low-level trajectory (Class 1) and medium-level trajectory (Class 2) were still significantly associated with lower 60-day mortality risk (Class 1: HR = 0.17, 95% CI = 0.07-0.41, $p < 0.001$; Class 2: HR = 0.26, 95% CI = 0.12-0.56, p = 0.001). The U-shaped trajectory (Class 3) still showed

no significant difference in 60-day mortality compared with the reference group (HR = 0.56, 95% CI = 0.14-2.25, p = 0.416).

Kaplan-Meier curves analysis

Kaplan-Meier (KM) survival curves stratified by serum calcium trajectory subgroups are presented in Figure 2. The results showed that the high-level trajectory (Class 4) had the lowest 60-day survival probability, while the low-level trajectory (Class 1) had the highest, followed by the medium-level trajectory (Class 2). Although the survival curve of the U-shaped trajectory (Class 3) intersected with those of Class 1 and Class 2 around weeks 2–3, the log-rank test indicated significant difference in survival probabilities among the four subgroups (p = 0.0082).

Sensitivity Analysis

Given the lack of significant difference in 60-day survival rates between Class 3 and Class 4, we compared serum calcium levels across the trajectory classes at various time points. As shown in Table 5, Class 1 consistently exhibited lower serum calcium levels on days 1, 3, 5, and 7, as well as lower mean, minimum, and maximum values during hospitalization compared to the other three classes. The initial values for Class 2 were lower than those for Class 3 during the first three days, became comparable by day 5, and subsequently dropped below Class 3 by week three. Class 3 initially had higher values than Class 4 over the first three days, followed by a gradual decline and subsequent rise, while remaining consistently lower than Class 4. When stratifying the population by 60-day mortality and comparing serum calcium levels between survivors and non-survivors at multiple time points, no significant differences were observed (all p > 0.05) (Supplementary Table 2). These findings suggest that Class 3 and Class 4 share similar prognostic characteristics attributable to their consistently elevated calcium levels.

Based on the similar prognostic characteristics between the U-shaped trajectory (Class 3) and the high-level trajectory (Class 4) identified in the primary analysis, we merged these two classes into "Group 3" and reclassified the low-level trajectory (Class 1) and medium-level trajectory (Class 2) as "Group 1" and "Group 2", respectively. Multivariable Cox regression analysis with Group 3 as the reference group (Supplementary Table 3) showed that after adjusting for the same covariates, Group 1 (HR = 0.21, 95% CI = 0.10–0.45, p < 0.001) and Group 2 (HR = 0.30, 95% CI = 0.15–0.61, p = 0.001) still had significantly lower 60-day mortality risk. KM survival curves for the three reclassified groups confirmed that Group 3 had the lowest 60-day survival probability (Supplementary Figure 2), with a statistically significant difference among the three groups (overall p = 0.0091).

To evaluate the robustness of the observed associations to unmeasured confounding, an E-value analysis was performed. The E-value for the point estimate of the association between serum calcium trajectories and 60-day mortality was 2.494 (95% CI: 1.492–4.051). This relatively large E-value indicates that an unmeasured confounder would need to have a strong association with both serum calcium

trajectory and 60-day mortality (with a risk ratio of at least 2.494) to fully explain the observed association, suggesting that the study results are robust to potential unmeasured confounding.

Discussion

To the best of our knowledge, this is the first study to identify heterogeneous serum calcium trajectories in **critically ill MM patients** using Latent Class Growth Modeling (LCGM) and to systematically explore the association between these dynamic trajectories and 60-day mortality. This work addresses a critical gap in the existing literature, which has predominantly focused on static baseline serum calcium levels in newly diagnosed or stable MM patients[6] [21], rather than capturing the dynamic fluctuations inherent to critical illness, characterized by complex interactions between myeloma-related bone resorption, acute kidney injury, sepsis, and intensive care interventions[4, 22].

Our findings indicate that the overall 60-day mortality rate among critically ill MM patients was 24.02%, which is lower than the 30-day mortality rate (35.2%) reported by Hampshire et al. [23] in a cohort of hematologic malignancy patients admitted to UK ICUs, but slightly higher than the in-hospital mortality rate (19.4%) reported by Mao et al. in critically ill MM patients[6]. This discrepancy is likely multifactorial: first, the choice of endpoint (60-day mortality vs. 30-day/in-hospital mortality) captures a longer follow-up period, including post-discharge deaths that may be associated with unresolved organ dysfunction or disease progression; second, variations in cohort severity; third, differences in healthcare settings and treatment patterns (e.g., utilization of novel anti-myeloma agents or renal replacement therapy) between study populations may further explain the variance[21].A key novel finding of this study is the identification of four distinct serum calcium trajectories over the first 28 days of ICU hospitalization, with clear prognostic stratification. Specifically, patients with low-level (Class 1) and medium-level (Class 2) trajectories exhibited significantly lower 60-day mortality (HR = 0.17 and 0.26, respectively, in the fully adjusted model) compared to those with high-level (Class 4) trajectories. Notably, the U-shaped trajectory (Class 3), characterized by an initial high calcium level, transient decline, and subsequent rise, showed no significant mortality difference from the high-level trajectory (HR = 0.56, p = 0.416). This observation is crucial. It suggests that even a transient normalization of serum calcium does not mitigate the adverse prognosis portended by the occurrence of hypercalcemia in the critical care setting[21] [24], but extends these findings by demonstrating that dynamic trajectory patterns, rather than single-point measurements, provide a more robust prognostic assessment.

Elevated serum calcium levels are inversely correlated with survival in MM patients [25], a relationship deeply rooted in the disease's biological aggressiveness and organ-damaging sequelae. This correlation is primarily driven by the intimate link between hypercalcemia and skeletal-related events (SREs)—including pathological fractures, extensive osteolytic lesions, renal impairment, and increased infection risk-all of which independently worsen prognosis [25, 26]. Mechanistically, MM-related hypercalcemia is predominantly mediated by osteoclast hyperactivation, a process amplified by myeloma cell-derived cytokines such as IL-6 and TNF-α that disrupt the bone remodeling balance, leading to unregulated bone resorption and calcium release into the circulation [24, 27]. Notably, this cytokine-driven bone destruction

is not only a cause of hypercalcemia but also a hallmark of high-risk MM biology, as these cytokines simultaneously promote myeloma cell proliferation and immune suppression[27].

Although the full spectrum of mechanisms by which hypercalcemia impairs survival remains incompletely elucidated, accumulating evidence highlights its association with adverse biological features. The presence of hypercalcemia at diagnosis is an established independent poor prognostic factor, with nearly 20% of newly diagnosed symptomatic MM patients presenting with this complication[28]. Critically, hypercalcemia in MM is strongly linked to high-risk cytogenetic abnormalities —including del 13q (detected by fluorescence in situ hybridization) and amp1q21, which are themselves associated with rapid disease progression, treatment resistance, and shortened overall survival [3]. The prognostic significance of hypercalcemia persists across age groups and treatment modalities, including conventional chemotherapy and novel agents such as thalidomide, lenalidomide, and bortezomib, suggesting that hypercalcemia is not merely a clinical manifestation but a surrogate marker of inherently aggressive disease biology and potential drug tolerance[3].

This biological context provides critical insights into the four serum calcium trajectories identified in our study. The high-level trajectory (Class 4), characterized by persistently elevated calcium levels—likely reflects uncontrolled myeloma activity, driven by high-risk cytogenetic profiles and sustained osteoclast-mediated bone destruction[3] [24]. These patients may harbor clones with inherent resistance to anti-myeloma therapies, as evidenced by the failure to normalize calcium levels despite intensive care interventions. Similarly, the U-shaped trajectory (Class 3), with initial hypercalcemia, transient reduction, and subsequent rebound, suggests a temporary response to acute interventions (e.g., hydration, bisphosphonates, or short-course anti-myeloma therapy) followed by disease progression or acquired drug resistance [30]. The recurrence of hypercalcemia in this trajectory aligns with the notion that cytogenetically driven bone destruction is not fully reversible with standard therapies, leading to persistent organ damage and poor outcomes comparable to those with sustained hypercalcemia[3, 22].In contrast, the low-level (Class 1) and medium-level (Class 2) trajectories, characterized by stable calcium levels within or below the normal range, are indicative of better disease control and treatment sensitivity.

These trajectories likely represent patients with non-aggressive disease biology (e.g., absence of high-risk cytogenetics), effective suppression of myeloma-driven cytokine production, and responsive bone remodeling following treatment. The stability of calcium levels in these groups suggests durable control of both myeloma cell proliferation and osteoclast activity. Notably, the segmented linear distribution of average calcium levels across trajectories (Class 1 < Class 2 < Class 3 < Class 4) mirrors the gradient of prognostic risk, consistent with Mao et al.'s observation of a nonlinear relationship between calcium levels and mortality [6]. This continuity further validates that serum calcium trajectories are not arbitrary groupings but reflect a biological spectrum of disease aggressiveness, from well-controlled to refractory disease. Collectively, our findings highlight the direct clinical applicability of dynamic serum calcium trajectory monitoring. In the ICU setting, these trajectories can function as an early-warning biomarker, prompting clinicians to intensify management of myeloma-specific complications, such as escalating

bone-targeted therapy or reassessing anti-myeloma regimens, when a persistently high or rebounding pattern is observed. Incorporation of trajectory analysis with validated severity scores may enhance risk stratification and support timely clinical decision-making.

This study has several notable strengths. First, it innovatively applies LCGM to characterize serum calcium trajectories in critically ill MM patients, shifting the focus from static to dynamic biomarker assessment, a paradigm increasingly recognized in critical care research. Second, the use of hierarchical multivariable Cox regression and E-value analysis (E = 2.494) enhances the robustness of the observed associations against confounding factors. Third, the identification of prognostic trajectories provides a practical tool for risk stratification, addressing the unmet need for dynamic monitoring guidance in critically ill MM management.

Despite these insights, our study has several limitations that warrant consideration. First, the reliance on a single-center public database (MIMIC-IV) precluded access to detailed cytogenetic data (e.g., del 13q, amp1q21), bone marrow biopsy results, and long-term treatment response data—critical variables needed to directly validate the link between trajectories, high-risk biology, and treatment resistance. Future prospective studies should integrate these variables to explicitly test whether trajectory patterns correlate with specific genetic signatures and treatment outcomes. Second, the small sample size of the U-shaped trajectory group limits the statistical power to explore subgroup-specific mechanisms, such as differences in drug resistance patterns or organ damage trajectories. Larger multi-center cohorts are needed to confirm the clinical significance of the U-shaped pattern and identify potential interventions to prevent calcium rebound. Third, while E-value analysis (E = 2.494) supports the robustness of our findings to unmeasured confounding, residual factors such as bisphosphonate use, nutritional status, and fluid balance—all of which can influence serum calcium levels—were not fully accounted for. Future analyses should incorporate these variables to refine trajectory modeling and strengthen causal inferences. Finally, the retrospective design limits our ability to assess the impact of targeted interventions (e.g., early intensification of anti-myeloma therapy) on trajectory modification and survival. Prospective interventional studies are needed to determine whether altering unfavorable trajectories (e.g., preventing calcium rebound in Class 3) improves outcomes in high-risk critically ill MM patients.

Conclusion

In conclusion, this study demonstrates that dynamic serum calcium trajectories, modeled via LCGM, are robust, independent prognostic markers for 60-day mortality in critically ill MM patients. A key insight is the heterogeneous prognostic significance of hypercalcemia: sustained high-level or U-shaped (rebound) trajectories identify patients with the poorest outcomes, likely reflecting aggressive disease biology or treatment resistance. In contrast, stable low-to-medium trajectories are associated with significantly improved survival. These findings support a paradigm shift from static calcium assessment to dynamic trajectory monitoring, positioning serial calcium measurement as a real-time biomarker for disease activity in the ICU. Integrating this approach with conventional severity scores may refine early risk stratification and guide personalized management.

Abbreviations

Multiple myeloma (MM)、Latent Class Growth Modeling (LCGM)、Latent Class Growth Modeling (LCGM)、Intensive Care Unit (ICU)、International Classification of Diseases (ICD)、Structured Query Language (SQL)、Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)、Akaike Information Criterion (AIC)、Bayesian Information Criterion (BIC)、Sample-adjusted BIC (SABIC)、Lo-Mendell–Rubin (LMR)、Acute Physiology Score III (APSIII)、Simplified Acute Physiology Score II (SAPSII)、Oxford Acute Severity of Illness Score (OASIS)、Sequential Organ Failure Assessment (SOFA)、Hazard Ratio (HR)、Confidence Interval (CI)、Kaplan-Meier (KM)、Skeletal-related events (SREs)、White blood cell (WBC)、Blood urea nitrogen (BUN)、Platelet (PLT)、International Normalized Ratio (INR)、Prothrombin Time (PT)、Activated Partial Thromboplastin Time (APTT)、Heart rate (HR)、Beats per minute (bpm)、Systolic blood pressure (SBP)、Diastolic blood pressure (DBP)、Respiratory Rate (RR)、Oxygen saturation (SpO_2)、Creatinine (Cr)、Sodium (Na)、Potassium (K)、Anion gap (AG)、Bicarbonate (HCO_3^-)、Chloride (Cl^-)、Glucose (Glu)、Hematocrit (HCT)、Hemoglobin (Hb)、Interleukin-6 (IL-6)、Macrophage inflammatory protein-1α (MIP-1α)、Tumor necrosis factor-α (TNF-α)、Fluorescence in situ hybridization (FISH).

Declarations

Author contributions

Yan Zeng: Writing-original draft, Writing-review & editing, Data curation, Methodology. Xiaomin Cheng: Writing-original draft, Data curation, Methodology.

Yongran Si: Data curation, Validation. Jun Wang: Formal analysis, Software, Visualization. Jingwei Zhang: Writing-review & editing, Conceptualization, Investigation, Supervision. All authors read and approved the final manuscript.

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Data accessibility

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author. Data in the article can be obtained from mimic-IV data-

base (https://mimic.mit.edu/)

Ethical considerations

The study utilized data from the MIMIC (Medical Information Mart for Intensive Care) database, which is a publicly available dataset that does not require individual ethical approval. The data are de-identified

and anonymized, ensuring that no personally identifiable information can be linked to individual participants. Therefore, ethical approval was not required for this study. There was no requirement of individual informed consent to extract data from the mimic-IV database because mimic-IV database information was publicly available and all patient data were deidentified

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to polish. After using this tool or service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

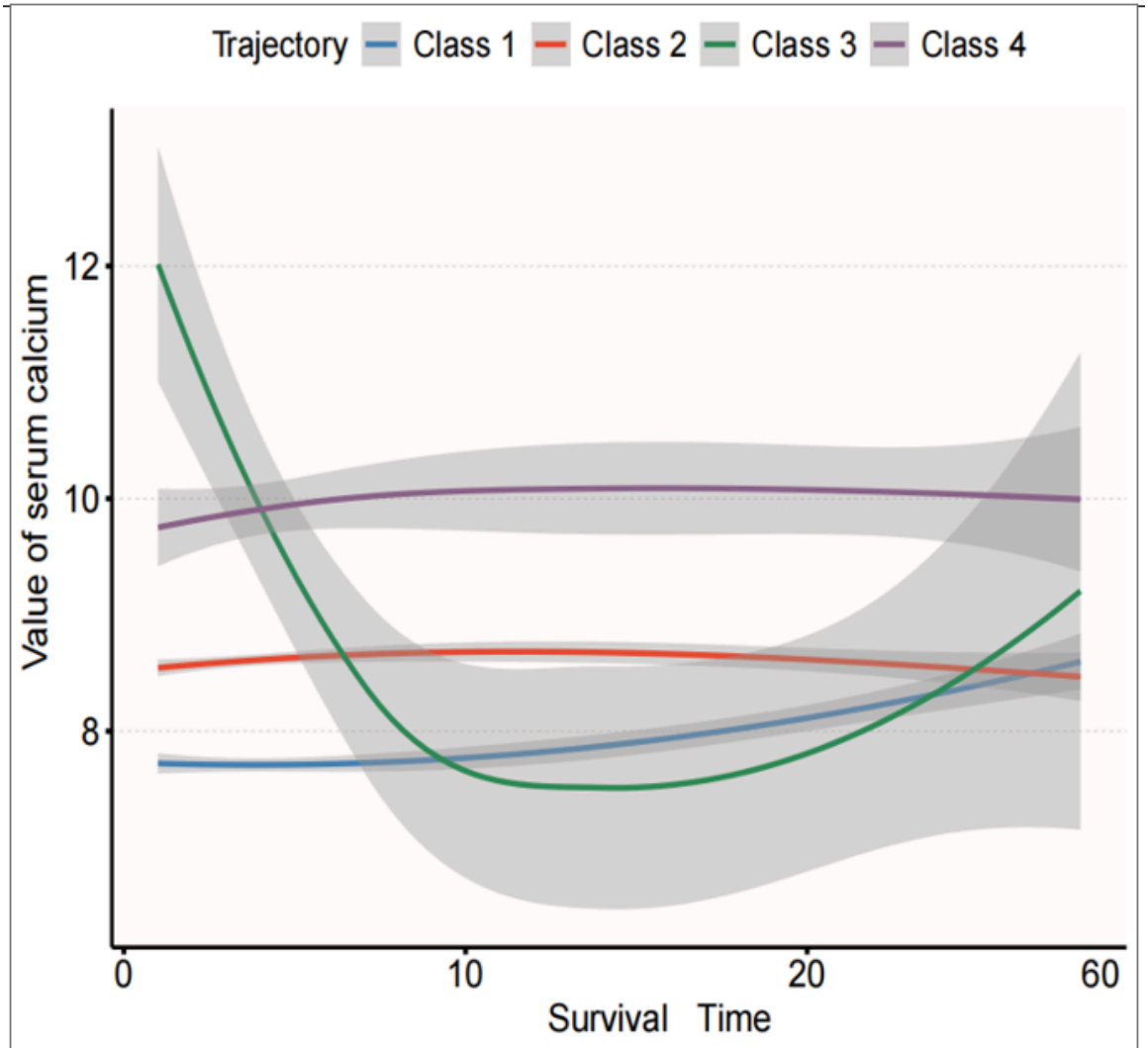


Fig 1. Trajectory curve. The figure illustrates the various trajectories of serum calcium values over survival time in critically ill patients. The curves are divided into four classes (Class 1 to Class 4), each representing a distinct pattern of serum calcium variation. The vertical axis depicts the value of serum calcium, while the horizontal axis represents survival time (in days). Each class's curve demonstrates the changes in serum calcium levels at different time points, accompanied by a shaded region indicating the estimated confidence interval.

Figure 1

See image above for figure legend.

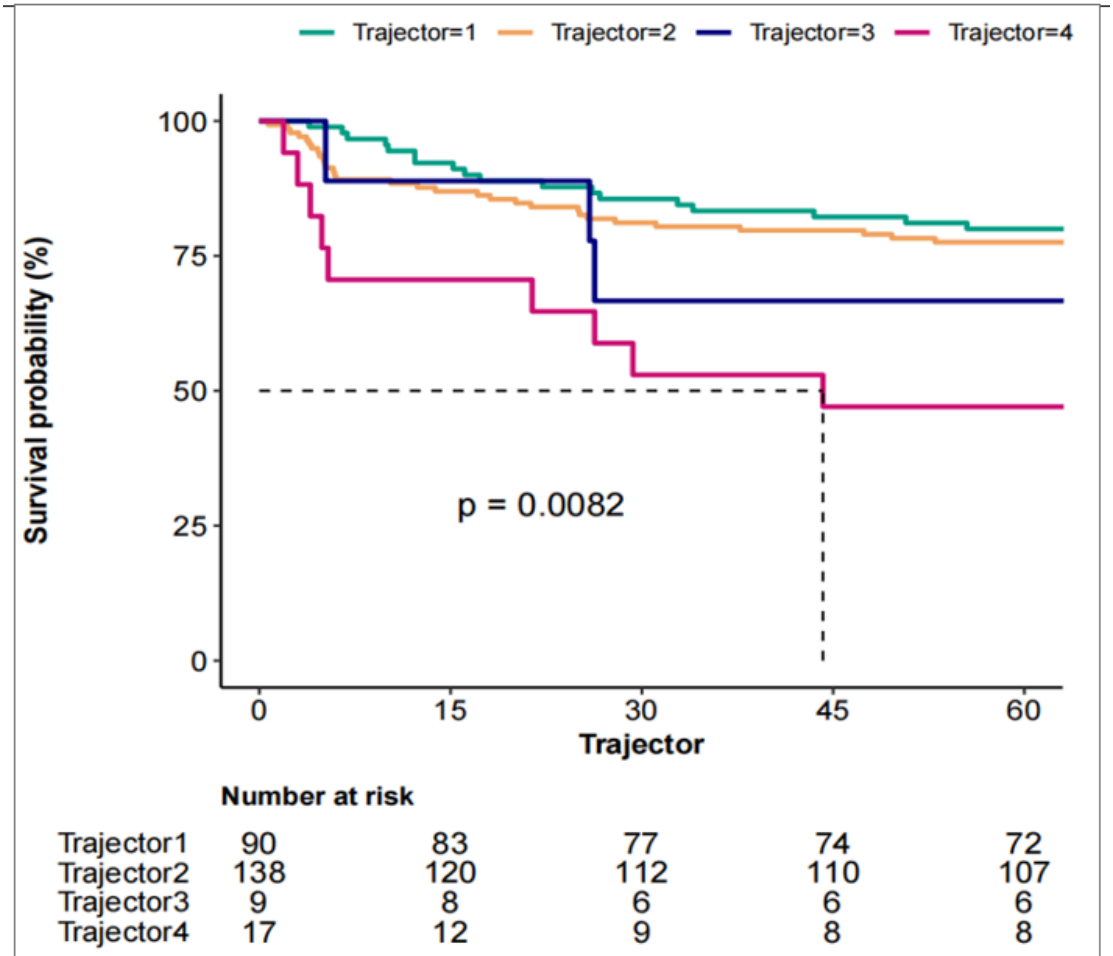


Fig 2. KM curves for different trajectories.

The figure illustrates the survival probabilities of four different serum calcium change trajectories. The vertical axis represents survival probability (%), while the horizontal axis indicates the trajectory classes. The curves of different colors correspond to distinct trajectory classes (Trajectory 1 to Trajectory 4). The graph reveals significant differences in survival probabilities over time, with Trajectory 4 (in pink) showing the lowest survival probability, falling below 50% around 45 days. The p-value of 0.0082 indicates that the differences in survival rates among the trajectories are statistically significant. The table below lists the number at risk for each trajectory at different time points.

Figure 2

See image above for figure legend.

Supplementary Files

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

- Table1to5.docx
- supp.docx