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Dynamic changes in mean corpuscular volume could be integrated into longitudinal prediction frameworks for individualized risk assessment in the ICU setting: A retrospective study

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Abstract

Objective: To evaluate whether early variability in mean corpuscular volume (MCV) during the first five days of intensive care unit stay is associated with in-hospital mortality in critically ill patients. **Methods:** We retrospectively studied all adult patients treated on intensive care units (ICU) at the University Medical Center Mannheim between 2018 and 2022 with more than one MCV measurement within the first five days, including at least one on the day of admission. The primary endpoint was in-hospital mortality. MCV variation, expressed as the coefficient of variation (CV), was analyzed using generalized additive models, multivariable logistic and Cox regression. **Results:** Among 5,327 patients (median age 66 years, 38.9% female, mortality 28.3%), median MCV variation was 1.86% (IQR 1.15–2.74%). Patients with high variation (CV >2.5%) showed higher mortality rates (34.7% vs. 20.1%, p<0.0001). In a baseline-adjusted model, this association remained significant (OR 1.65, 95% CI 1.46–1.87, p<0.001). By contrast, baseline MCV at admission showed a univariat association with mortality but was not independently associated with mortality after multivariate adjustment (OR 1.02, 95% CI 0.98–1.06, p=0.31). Determinants of high variation (>2.5%) included elevated CRP, transfusion volume, respiratory disease, and fluid balance disturbances. In a second, severity-adjusted model including lactate, mean arterial pressure, and fluid balance, the previously observed association between high MCV variation and mortality was no longer significant (adjusted OR 1.16, p =

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0.57, CI: 0.84–1.59). **Conclusions:** Early variation in MCV during the initial five days after ICU admission is associated with in-hospital mortality in unadjusted analyses. However, this relationship is not independent of established clinical severity markers, suggesting that MCV variability reflects disease severity. Nonetheless, MCV variation may serve as a readily accessible adjunctive marker of physiological instability in critically ill patients, meriting further investigation.

Keywords
MCV, mean corpuscular volume, variation, intensive care medicine, prediction

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Introduction

Early identification of patients at high risk for adverse outcomes remains a key challenge in the critical care setting. Patients treated in intensive care units (ICUs) vary in clinical presentation, treatment response and outcomes, and timely prognostication is important to support clinical decisions and resource allocation.[1]

Although a variety of scores are available to prognosticate outcomes, their implementation in clinical routine is often limited by the number and availability of required variables, the need for specific biomarkers, and associated workflow complexity. Therefore, biomarkers that are easily accessible and routinely collected remain of particular interest, if they offer prognostic information without adding burden to clinical workflows. Among biomarkers frequently collected during ICU care, red blood cell indices including mean corpuscular volume (MCV) are standard components of complete blood counts and provide insights beyond underlying hematological disorders.[2] MCV reflects the average volume of circulating erythrocytes, which are terminally differentiated cells with a lifespan of approximately 120 days; therefore, short-term changes in MCV primarily result from shifts in erythrocyte population composition rather than true volumetric changes of individual cells.[3] In patients with intracerebral hemorrhage, MCV at admission was associated with 30-day mortality and which was highest among those with MCV $\geq$ 92fl.[4]

Compared to single biomarker values, dynamic changes of these values have been shown to better predict mortality in critically ill patients. As an example, increasing levels of arterial lactate within the first 24 hours of ICU admission have been identified as a strong predictor of hospital mortality.[5] Similarly, changes in neutrophil-to-lymphocyte-to-platelet ratio during the initial 48 hours of ICU care are significantly associated with mortality.[6] Moreover, increasing levels of procalcitonin over the first three days of ICU treatment is an independent predictor of mortality.[7,8] These results indicate that temporal changes in biomarker levels provide additional prognostic information that may enhance single-point measurements.

Previous studies have suggested associations between MCV values and adverse clinical outcomes, including increased mortality in certain patient populations.[9–14] For instance, one study demonstrated that MCV values on admission are positively associated with 30-day mortality in patients with intracerebral hemorrhage, with a 1 unit increase in MCV (measured in femtoliter) indicating a 3% increase in 30-day mortality.[4] Dynamic changes in MCV values during the early ICU stay may reflect underlying processes including changes in intravascular volume or inflammation, all of which are relevant in critical illness.[15]

To date, the prognostic value of MCV variation in critically ill patients remains poorly understood. There is a lack of evidence regarding whether early fluctuations in MCV are independently associated with in-hospital mortality, and whether this association remains consistent across different thresholds of variation. Furthermore, no studies have systematically examined MCV variability as a potential prognostic marker within the first days of ICU admission.

The aim of this retrospective cohort study was to investigate the association between MCV variation during the first five ICU days and in-hospital mortality in a large cohort of critically ill patients. In addition, we sought to evaluate the robustness of this association by applying multiple variation thresholds and to explore potential clinical determinants and implications of elevated MCV variability.

Methods

General methods

This study is a retrospective, observational cohort study that included all patients who underwent treatment at one of our ICUs from 01/2018 to 05/2022 at the University Medical Center Mannheim, Germany. This study is reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines.[16] The study was carried out according to the principles of the 1975 Declaration of Helsinki as revised in 2024 and was approved by the Medical Ethics Commission II of the Faculty of Medicine Mannheim, University of Heidelberg, Germany (Institutional review board

approval number 2025-810-AF 11, approval date: 25 February 2025). The requirement for informed consent was waived due to the retrospective nature of the study.

Study population

The study included all patients treated in one of the ICUs (either medical or surgical) between January 2018 and May 2022 who were 18 years or older and with an ICU length of stay of at least 24 hours. Patients without MCV values on admission and those with less than two MCV measurements on at least two separate days within the first five days of ICU stay were excluded. The remaining patients formed the 'final study cohort'.

Data extraction

All patient data collected during hospital stays were recorded in a patient data management system at the Data Integration Center of the University Medical Center Mannheim, Germany. Also, all patient data were fully de-identified prior to analysis, and no information allowing direct or indirect identification of individual patients was available to the investigators. The data included vital parameters, medication, laboratory parameters and outcomes. ICD-10 codes were assigned after a thorough review of all available data post-discharge and was obtained from the Medical Controlling department of the University Medical Center Mannheim (Supplemental Table 1). The data were then transferred to a relational database and specific data points were retrieved using Structured Query Language.

Data preparation

To facilitate temporal analysis, each ICU stay was segmented into 24-hour intervals, starting at the time of ICU admission. All dynamic variables were aggregated within each 24-hour block, defined relative to the individual admission time, using their maximum, minimum, median and mean values.

Variables were categorized as either static or dynamic. Static variables (which remained constant throughout the ICU stay) included age, source of admission, body mass index (BMI) and sex. Dynamic variables (which varied during the ICU stay) encompassed vital parameters and laboratory values. All variables were evaluated for plausibility. Valid ranges were clinically defined in consultation with an experienced intensive care physician. Measurements falling outside of these pre-defined valid ranges were excluded from the analysis (Supplemental Table 2).

Ventilator therapy was quantified by the cumulative duration since the last initiation of ventilation. Fluid therapy was assessed by calculating both the daily fluid balance and the total fluid balance for the entire patient stay. Renal replacement therapy (RRT) was encoded as a binary variable, indicating its presence or absence on each stay day. No imputation of missing values was performed. Analyses were conducted using available-case data to ensure that only observed measurements contributed to the results.

Study endpoint

In-hospital mortality was selected as the study endpoint to assess the predictive performance of MCV variation in critically ill patients.

Statistical analysis

Statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC, USA), GraphPad Prism Version 9.2.0 (GraphPad Software, La Jolla, CA, USA), and R Statistical Software Version 4.2.3 (R Core Team, 2024).[17]

Data for continuous variables are reported as median ± interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. Qualitative parameters were analyzed using a 2×2 contingency table and chi-squared test or Fisher's exact test as appropriate. Correlations between continuous variables were assessed by calculating Spearman's rank correlation coefficient (Spearman's p) or Pearson's correlation coefficient (Pearson's r).

We applied a Generalized Additive Model (GAM) analysis to investigate nonlinear associations between MCV variability and in-hospital mortality, using the coefficient of variation (CV) of MCV as the primary measure of variability. Smooth splines were used to capture complex patterns in the relationship. In addition, we used GAM to explore mortality risk across subgroups stratified by MCV variation. A logistic regression model was used to evaluate the association between MCV variation within the first five days and in-hospital mortality. Variables included in the multivariable logistic regression were selected *a* priori based on their known or suspected pathophysiological relevance to MCV variability and mortality in

critically ill patients The primary model was adjusted for baseline characteristics, including age, ICU length of stay, number of MCV measurements, and baseline MCV values, and included MCV variation (>2.5% vs. ≤2.5%) as the main predictor variable. To further explore whether the observed association was independent of underlying disease severity, we fitted an extended model additionally adjusted for established physiological severity markers (including lactate, mean arterial pressure, and fluid balance). This second model was designed to assess potential mediation effects and to test whether MCV variation remained an independent predictor after accounting for these parameters.

McFadden's R^2 was used to assess the goodness of fit of the logistic regression model. Discriminative ability was further assessed by constructing receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC) with 95% confidence intervals. To assess the stability of variable selection and identify the most robust predictors of mortality, we additionally performed penalized regression using the least absolute shrinkage and selection operator (LASSO) with 10-fold cross-validation.

Kaplan-Meier survival curves were generated to compare survival according to the MCV variation and differences in survival were assessed using the log-rank test. Statistical significance for all tests was set at a two-tailed p-value of less than 0.05. To account for multiple testing, all p-values were adjusted using the false discovery rate (FDR) according to Benjamini-Hochberg.

Cutoff definition and classification of MCV variation

To classify patients according to early MCV variation, we calculated the maximum percentage deviation from baseline MCV during the first five ICU days. This time frame was chosen to capture early physiological dynamics while minimizing confounding from prolonged ICU courses and treatment-related effects and to include a larger proportion of patients with shorter ICU stays. Baseline MCV was defined as the mean MCV available measurement on ICU day 0 (i.e. within the first 24 hours after ICU admission). The maximum variation was determined as the largest absolute difference between the baseline and any subsequent mean MCV value within the first five days, expressed as a percentage of the baseline. Both increasing and decreasing MCV trajectories were observed, supporting variability rather than direction as the relevant signal. A threshold of 2.5% was selected as a pragmatic cut-point, guided by the upper quartile of the MCV coefficient-of-variation (CV) distribution observed in the study population. This threshold was then applied to the maximum absolute percentage deviation from the day-0 baseline MCV to define high (>2.5%) versus low (≤2.5%) variation groups.

Patients were included in this analysis only if they had at least two MCV measurements within the first five ICU days, including at least one on day 0 and another obtained after day 0.

Results

Cohort description and baseline characteristics

The study included 9,109 ICU patients between January 2018 and May 2022. After applying exclusion criteria, the final study cohort consisted of 5,327 patients (Figure 1(a)). The median age was 66 years (IQR 55–76), and 2,857 patients (38.9%) were female. The overall in-hospital mortality rate was 28.3%. When comparing both MCV-variation groups, patients with >2.5% variability showed a substantially higher burden of critical illness, including higher rates of renal replacement therapy (8.3% vs. 17.5%), invasive or non-invasive ventilation (35.2% vs. 65.4%), and prolonged ICU stay (>5 days: 24.4% vs. 59.5%) (all $p < 0.001$ after FDR adjustement). Baseline characteristics of the study cohort are summarized in Table 1.

Prognostic utility of MCV at admission

First, we assessed the prognostic utility of a single MCV value determined at or close to ICU admission. The distribution of available MCV values on admission in our study cohort is shown in Supplemental Figure 1.

Patients were classified as either with normal (4,021 patients, 75.5 %) or with abnormal MCV values (1,306 patients, 24.5 %) on admission. Mortality was slightly but significantly higher in patients with abnormal MCV values, compared to those with normal MCV values (30.9% vs. 27.9%, p=0.016, Figure 1(b)). The observed effect size was small (Cohen's d = –0.078).

Kaplan-Meier analysis confirmed the observed differences in survival between both groups (log-rank $p = 0.047$; Figure 1(c) and (d)). Finally, cox regression analysis revealed a 12.2% higher mortality hazard in patients with abnormal MCV values on admission (HR = 1.12, 95% CI: 1.00–1.27, $p = 0.047$). Consistently, receiver operating characteristic (ROC) analysis demonstrated poor discriminative performance of admission MCV values for predicting in-hospital mortality (AUC = 0.52, 95% CI: 0.50-0.54, Supplemental Table 3). In summary, although admission MCV values showed a

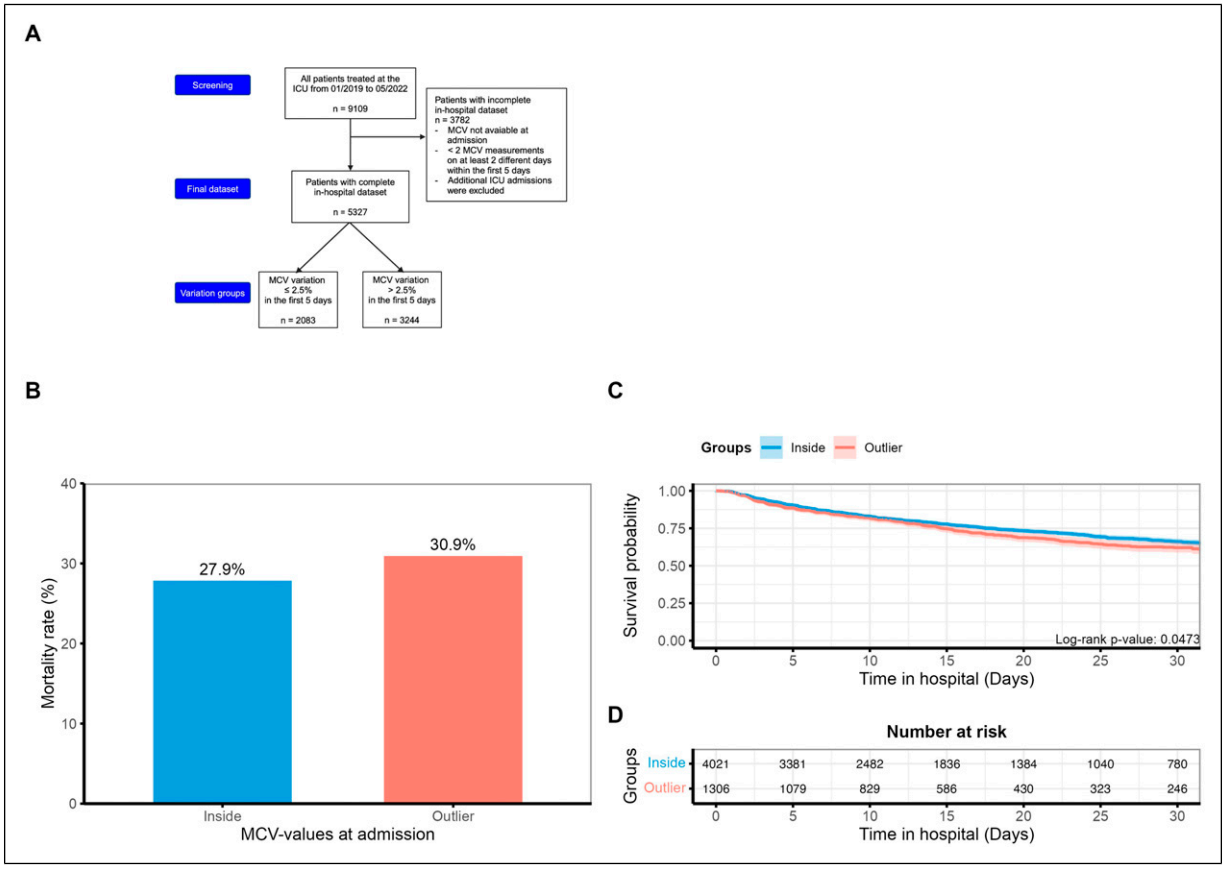

Figure 1. Cohort selection and prognostic value of admission MCV.
(a) Study flow diagram showing screening, exclusions and the final cohort (n = 5,327). For downstream analyses, patients were grouped by early MCV variation within the first five ICU days (≤2.5% vs. >2.5%). (b) Barplot with in-hospital mortality by admission MCV: patients with MCV **outside** the reference range ("Outlier") had higher mortality than those **inside** the range (30.9% vs. 27.9%). (c) Kaplan–Meier curves for time to in-hospital death by admission MCV group (log-rank p = 0.0473). (d) Number-at-risk table corresponding to panel C, demonstrating the progressive decline in patient numbers over the hospitalization period due to discharge or death.

statistically significant univariate association with mortality, the effect size was minimal, discriminative performance poor, and the association did not persist after multivariable adjustment, underscoring limited clinical relevance.

Association between early MCV variation and in-hospital mortality

Second, we assessed whether MCV variation was associated with in-hospital mortality. To this end, MCV variability was assessed by calculating the maximum coefficient of variation (CV) within the first five ICU days (Figure 2(a)). The distribution of CV was right-skewed (median: 1.86%, IQR: 1.15–2.74%), and non-survivors had significantly higher CV values within the first days and throughout the entire ICU stay than survivors (2.16% vs. 1.71%, p<0.001 and 2.09% vs. 1.63%, p<0.001). A nonlinear association between CV and hospital mortality was found using a GAM model ($Chi^2 = 23.19$, $p < 0.001$; Figure 2(b)), although the visual impression suggests an approximately linear, monotonic increase. A similar association was observed when analyzing the entire ICU stay rather than just the first five days (Figure 2(c)).

Next, patients were stratified by MCV variation in a high (defined as CV >2.5%) and low (defined as CV ≤2.5%) variation group. This cutoff was selected based on the third quartile of CV distribution. High MCV variation was associated with an in-hospital mortality of 34.1%, compared to 20.1% for low MCV variation (Figure 3(a) and (b)). Boxplots depict the distribution of baseline MCV, maximum variation, and clinical course parameters across the two variation groups (Figure 3(c)). Patients with high MCV variation showed significantly higher maximum MCV variation values as well as longer ICU and hospital stays compared to those with low variation, whereas baseline MCV values did not differ significantly between groups. The observed effect sizes, however, were modest despite the statistical significance (all $p < 0.001$, except baseline MCV; Supplemental Table 3). Kaplan-Meier analysis revealed significantly reduced survival in the high MCV variation group (log-rank $p < 0.0001$; Figure 3(d) and (e)).

Table 1. Baseline characteristics.

	Final study cohort	MCV variation ≤ 2.5%	MCV variation > 2.5%
	n=5,327	n=2,083	n=3,244
Demographics and medical history			
Age (years), median (IQR)	66 (55-77)	67 (55-78)	66 (55-76)
Sex, No. (%)			
Female	2,116 (39.9)	819 (39.5)	1,297 (40.1)
Male	3,211 (60.1)	1264 (60.5)	1,947 (59.9)
BMI (kg/m^2), median (IQR)	26.1 (23.4-29.4)	25.9 (23.1-29.3)	26.1 (23.7-29.4)
Diabetes, No. (%)	1,768 (33.2)	646 (31.0)	1,122 (34.6)
Hypercholesterolemia, No. (%)	494 (9.3)	226 (10.8)	268 (8.3)
Arterial hypertension, No. (%)	1,806 (33.9)	721 (34.6)	1,085 (33.4)
Chronic kidney disease (any stage), No. (%)	1,433 (26.9)	676 (32.5)	757 (23.3)
Renal replacement therapy, No. (%)	740 (13.9)	173 (8.3)	567 (17.5)
NIV/IMV, No. (%)	2,855 (53.6)	733 (35.2)	2,122 (65.4)
Main diagnosis[1], No. (%)			
Digestive system disease	422 (7.9)	144 (6.9)	278 (8.6)
Nervous system disease	112 (2.1)	46 (2.2)	66 (2.0)
Trauma disease	550 (10.3)	188 (9.0)	362 (11.2)
Infectious and parasitic diseases	209 (3.9)	79 (3.8)	130 (4.0)
Circulatory system disease	1,792 (33.6)	776 (37.3)	1,016 (31.3)
Neoplasms disease	830 (16.6)	363 (17.4)	467 (14.4)
Respiratory system disease	836 (15.7)	235 (11.3)	601 (18.5)
Genitourinary system disease	150 (2.8)	66 (3.2)	84 (2.6)
Other	426 (8.0)	186 (8.9)	240 (7.4)
Admission category, No. (%)			
Medical	2,431 (45.6)	1,004 (48.2)	1,427 (44.0)
Scheduled surgery	368 (6.9)	185 (8.9)	183 (5.6)
Unscheduled surgery	1,782 (33.4)	661 (31.7)	1,121 (34.5)
Other	746 (14.0)	233 (11.2)	513 (15.8)
Admission source, No. (%)			
Emergency Room	2,049 (38.5)	807 (38.7)	1,242 (38.3)
Other ICU	384 (7.2)	105 (5.0)	279 (8.6)
Hospital ward	1,909 (35.8)	827 (39.7)	1,082 (33.3)
External hospital	716 (13.4)	209 (10.0)	507 (15.6)
Other	269 (5.0)	135 (6.5)	134 (4.1)
Length of ICU stay			
> 5 days, No. (%)	2,440 (45.8)	509 (24.4)	1,931 (59.5)
Length of ICU stay (days), median (IQR)	4.4 (2.5-9.5)	2.8 (1.9-4.9)	6.3 (3.5-12-9)
Mortality, No. (%)			
ICU mortality	987 (18.5)	223 (10.7)	764 (23.6)
In-hospital mortality	1,524 (28.6)	419 (20.1)	1,105 (34.1)

BMI, body mass index. ICU, intensive care unit. IQR, interquartile range. IMV, invasive mechanical ventilation. MCV, mean corpuscular volume. NIV, noninvasive ventilation.
[1]According to ICD-10 code, International Classification of Diseases codes, 10th revision, German modification.

Cox regression analysis confirmed increased hazard for in-hospital mortality in patients with >2.5% MCV variation (HR = 1.38, 95% CI: 1.23–1.54, $p < 0.001$). After adjusting for age, ICU length of stay, number of MCV measurements and baseline MCV, the association remained significant (adjusted HR = 1.65, 95% CI: 1.46–1.87, $p < 0.001$). ROC analysis yielded only modest discriminative performance (AUC = 0.61; 95% CI: 0.59-0.63, Supplemental Table 4), indicating that while MCV variation was significantly associated with hospital mortality in regression analyses, its standalone predictive accuracy was limited.

Clinical and biological determinants of MCV variation

Building on these findings, we next aimed to explore whether the observed association between MCV variation and mortality was independent of physiological disease severity. We therefore sought to identify clinical and biological determinants of

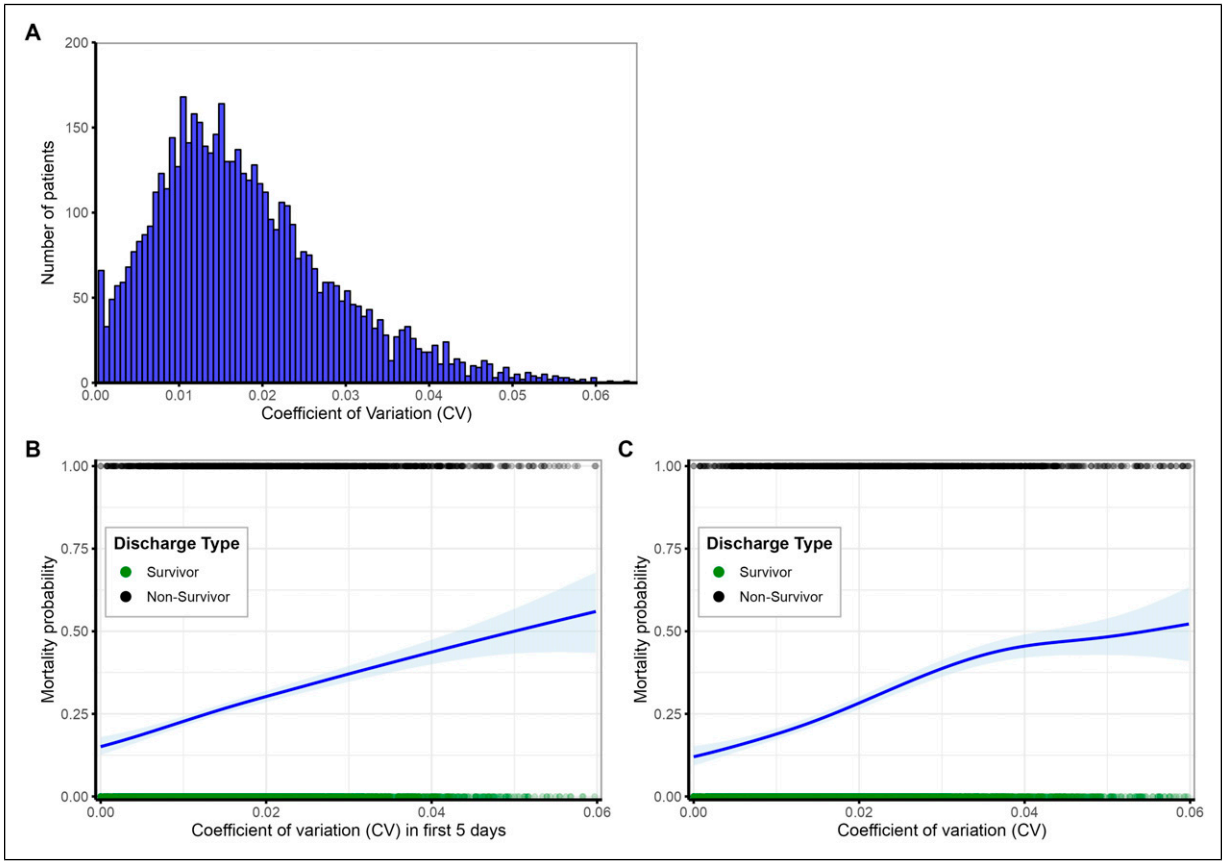

Figure 2. Distribution and association of early MCV variation with in-hospital mortality.
(a) Distribution of the coefficient of variation (CV) of MCV within the first five ICU days, demonstrating a right-skewed distribution in the study population. (b) Generalized additive model (GAM) showing a linear increase in mortality probability with rising MCV variation during the first five ICU days. The black dotted line above the plot area represents individual non-survivors, while the green dotted line along the x-axis represents survivors. (c) GAM illustrating a similar monotonic association when extending the analysis to the entire ICU stay. Black dots above the plot indicate non-survivors, and green dots below the x-axis indicate survivors.

high MCV variation (CV > 2.5%). A multivariate logistic regression identified maximum CRP (OR = 1.002, 95% CI: 1.001–1.004, $p < 0.001$), higher transfusion volume (OR = 1.70, 95% CI: 1.30–2.24, $p < 0.001$), respiratory disease (OR = 2.26, 95% CI: 1.32–3.92, $p < 0.05$) and disturbances in mean and maximum fluid balance per 24h (maximum fluid balance, OR = 1.0001, 95% CI: 1.000–1.0002, $p < 0.05$) as independent determinants of MCV variation (Figure 4(a), Supplement Table 5). In line with these findings, increased MCV variability was predominantly observed in patients with infectious and respiratory conditions and in those exposed to erythrocyte transfusions, whereas existing hematological disease was not associated with MCV variation (OR = 0.847, 95% CI: 0.547–1.298, $p = 0.672$, Figure 4(a)).

In a complementary analysis, we further examined the prognostic value of MCV variation after adjustment for established severity markers (including lactate, mean arterial pressure and fluid balance), which represent potential mediators of the observed association between MCV variation and mortality. In this extended model, MCV variation was no longer independently associated with in-hospital mortality (adjusted OR 1.16; $p = 0.57$, CI: 0.84-1.59), indicating that it largely reflects underlying physiological disturbances rather than acting as an independent predictor (Figure 4(b), Supplemental Table 6). Results were consistent when repeating the analysis using LASSO regression for variable selection, which retained a parsimonious predictor set dominated by lactate, SAPS (Simplified Acute Physiology Score), RASS (Richmond Agitation-Sedation Scale), hemoglobin, fluid balance and age (Supplemental Table 7).

Sensitivity analyses and threshold robustness

Importantly, we conducted multiple sensitivity analyses to assess the robustness of our results. Setting the CV MCV variation cutoff for group adjudication to 5.0% MCV CV yielded comparable results to the previously applied 2.5% threshold. At this threshold, 1,310 patients had high MCV variation, with a mortality rate of 38.9% vs. 25.2% in low MCV variation group

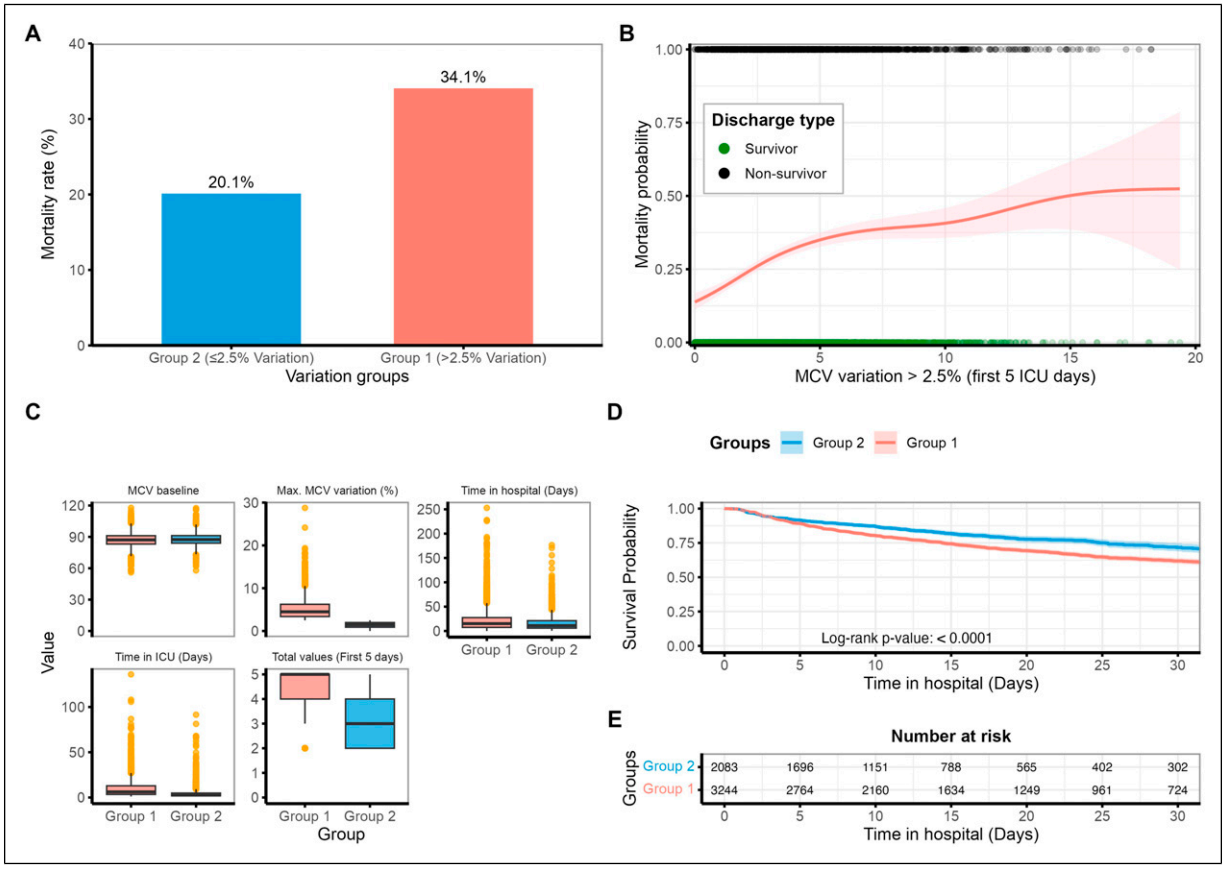

Figure 3. Association between early MCV variation (MCV ≤2.5% vs. >2.5%). and in-hospital mortality. (a) Barplot with In-hospital mortality stratified by early MCV variation. Patients with high variation (>2.5 %) had a markedly higher mortality compared to those with low variation (≤2.5 %). (b) Generalized additive model (GAM) showing an increasing mortality probability with higher MCV variation within the first five ICU days. The black dotted line above the plot represents non-survivors, and the green dotted line below the x-axis represents survivors. (c) Boxplots comparing baseline MCV, maximum MCV variation, ICU stay, hospital stay, and total number of MCV measurements within the first five days between groups with high and low MCV variation. (d) Kaplan–Meier survival curves showing reduced survival in patients with high MCV variation (log-rank $p < 0.0001$). (e) Number-at-risk table corresponding to panel D, illustrating the progressive decline in patient numbers during hospitalization due to discharge or death.

(CV ≤5.0%). GAM and ROC analysis (AUC = 0.61, 95% CI: CI 0.59–0.62) confirmed a modest predictive performance, indicating limited discriminative accuracy (Supplemental Table 4).

In further sensitivity analyses, the main findings remained consistent after exclusion of patients who received erythrocyte transfusions during the first five ICU days and after exclusion of patients with documented hematologic diseases (Supplemental Table 8, Supplemental Figure 2). In addition, restricting the analysis to patients with at least three available MCV measurements yielded comparable effect estimates, supporting the robustness of the observed association (Supplemental Table 3, Supplemental Figure 3).

Assessing differences in outcomes according to ICU length of stay revealed that patients with >2.5% MCV variation and prolonged ICU stay (>5 days) exhibited greater MCV variation. A detailed breakdown of this analysis is provided in Figure 4(c) and (d)). However, mortality rates between short and long ICU stays in this subgroup were not significantly different (35.1% vs. 33.2%, p = 0.26).

Taken together, MCV variation during the early ICU period is robustly associated with increased hospital mortality, but its individual predictive utility remains limited. The effect appears biologically plausible and consistent across thresholds and subgroups.

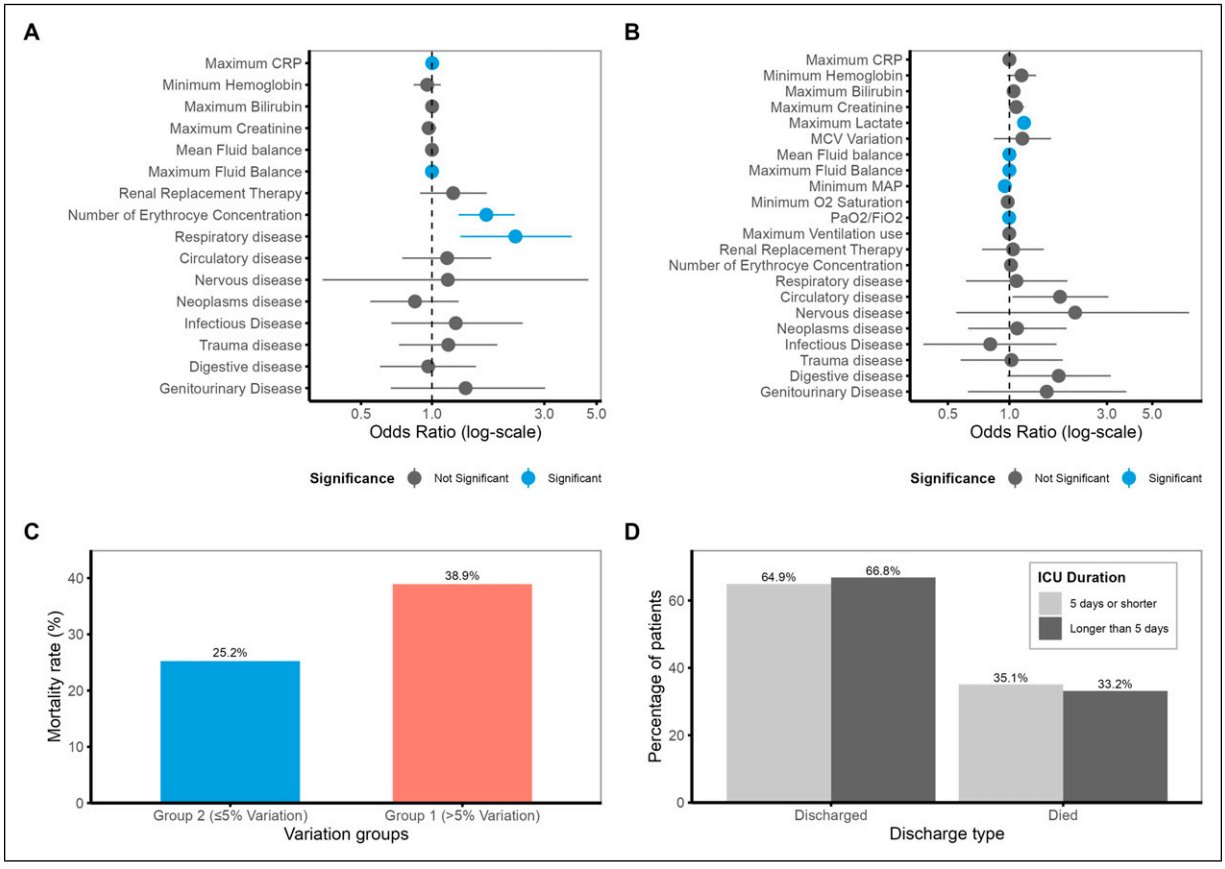

Figure 4. Determinants and robustness of the association between MCV variation and in-hospital mortality.
(a) Forestplot with multivariable logistic regression identifying independent clinical and laboratory determinants of high MCV variation (CV > 2.5 %). Significant predictors include elevated CRP, fluid balance disturbances, higher erythrocyte transfusion volume and respiratory disease. (b) Forest plot (extended mortality model adjusted for severity markers). After adjustment, MCV variation is not independently associated with in-hospital mortality. Significant covariates in this model include maximum lactate, mean fluid balance, maximum fluid balance, minimum MAP and PaO_2/FiO_2. (c) Sensitivity analysis using an alternative cutoff of 5 % for high MCV variation, showing a comparable increase in mortality (38.9 % vs. 25.2 %) to that observed with the primary 2.5 % threshold. (d) Comparison of discharge status by ICU stay length, demonstrating similar mortality between patients with short (≤5 days) and prolonged (>5 days) ICU stays within the high-variation subgroup (CV > 2.5 %).

Discussion

MCV is routinely measured as part of the complete blood count and is widely available across ICU settings, yet its dynamic changes over time have received limited attention in prognostic research. Based on early reports, we hypothesized that fluctuations in MCV during the first five days after ICU admission may reflect underlying pathophysiological processes such as inflammation, fluid shifts, or transfusion effects, and therefore could serve as a simple, non-invasive marker for mortality risk stratification. Notably, the attenuation of the association after adjustment for lactate, mean arterial pressure, and fluid balance suggests substantial overlap with shock-related severity information indicating that MCV variability likely acts as an integrated downstream signal of systemic stress (e.g., inflammation, transfusion exposure, and intravascular volume shifts) and should therefore be interpreted as an adjunct marker of disease severity rather than a standalone prognostic tool.

A threshold of 2.5% MCV variation was identified as a clinically meaningful cutoff, clearly differentiating between patients with higher and lower mortality risks. Patients with MCV variation above this value showed a significantly higher mortality rate indicating the potential importance of dynamic changes in erythrocyte indices during the early phase of ICU stay. Although the 2.5% threshold was empirically derived from the observed distribution of MCV variability in our cohort, it is important to contextualize this value in relation to known analytical and biological variation. Prior studies indicate that the analytical coefficient of variation for automated MCV measurements is typically below 1%, while intra-individual biological variation of MCV in stable conditions is low, generally in the range of 1–2%.[18–20] Thus, an early MCV deviation exceeding 2.5% is unlikely to be explained by measurement noise alone and may reflect acute alterations in erythrocyte population dynamics, such as transfusion effects, reticulocyte release, or fluid shifts commonly observed in critical illness.

In contrast, MCV measurements at admission showed limited prognostic capability. Although patients classified as 'outliers' (MCV values above the normal range) had higher mortality rates compared to those within the reference range, the predictive power remained relatively low.

This finding is in line with previous studies suggesting, that while MCV at a single time point may reflect underlying comorbidities, its isolated measurement does not robustly predict clinical outcomes.[9,11] These findings highlight the added value of a longitudinal analysis over isolated baseline measurements, as the dynamic trajectory of MCV appears to capture critical pathophysiological processes more accurately.

MCV in ICU prediction

Our findings align with previous studies that identified static MCV values as indicators of poor clinical outcomes, particularly in neurological conditions like intracerebral hemorrhage.[4] However, while earlier studies primarily focused on single MCV measurements, our analysis extends this understanding by incorporating dynamic variability over time. This approach reveals that MCV changes during ICU stay may serve as more robust prognostic markers than baseline values alone, supporting a more nuanced perspective as seen in recent investigations of dynamic biomarkers in critical care settings.[5,15]

The study by Rayes et al. (2019) demonstrated that elevated MCV was associated with increased mortality in cardiac ICU patients, yet static MCV at admission was not a strong predictor for in-hospital mortality, aligning with our observations.[11] Additionally, Hsieh et al. (2017) reported that higher baseline (static) MCV was independently associated with increased all-cause, cardiovascular, and infection-related mortality in patients with chronic kidney disease.[10] While Hsieh et al. examined static MCV rather than variability, their results support the broader notion that erythrocyte indices capture systemic pathophysiology relevant to mortality risk. This is consistent with our findings, where patients with high early MCV variability showed worse outcomes, likely reflecting multifactorial systemic disturbances.

Moreover, the work by Tang et al. highlighted that higher MCV was associated with increased 28-day mortality in sepsis patients, supporting the concept that MCV reflects both inflammation and erythropoietic stress in critical illness.[9] Our analysis confirms that not only baseline MCV but also its variation over time provides critical prognostic information, extending these observations to a broader ICU cohort. Although several variables reached statistical significance in multivariable models, some effect sizes were very small (e.g., CRP odds ratios close to 1). This likely reflects the large sample size and high statistical power rather than clinically meaningful effect magnitude, underscoring the need to distinguish statistical significance from clinical relevance when interpreting these associations.

The role of physiological variability in predicting outcomes in critically ill patients

Several studies have demonstrated that the variability of physiological parameters is a relevant predictor of clinical outcomes in critically ill patients. Brown et al. (2015) found that increased heart rate variability in patients with severe sepsis and septic shock was associated with faster vasopressor independence, indicating better hemodynamic stabilization.[21] Lanspa et al. (2014) showed that increased glucose variability was significantly correlated with 30-day mortality in critically ill patients receiving intravenous insulin, with a stronger association observed in non-diabetic patients.[22] Furthermore, Krinsley (2009) demonstrated that non-diabetic patients with high glucose variability had a significantly higher mortality risk, while those with low variability showed a markedly better prognosis.[23]

Our findings align with this evidence, highlighting that variability in MCV during the first five days after ICU admission is closely linked to in-hospital mortality. Similar to heart rate and glucose concentration, fluctuations in MCV values appear to be indicative of pathophysiological instability associated with poorer survival outcomes. This supports the hypothesis that dynamic changes in various physiological parameters can provide valuable predictive information beyond static measurements.

Mechanistic insights and pathophysiological considerations

The underlying mechanisms driving MCV variability in critically ill patients are likely multifactorial. Inflammatory responses, fluid shifts and alterations in erythropoiesis may contribute significantly to these changes. In critical illness, pro-inflammatory cytokines and fluid imbalances are known to alter red blood cell (RBC) morphology and distribution, potentially explaining the observed fluctuations in MCV.[2] This interpretation aligns with the clinical profile of patients with high MCV variability, who showed a greater burden of critical illness, including higher rates of renal replacement therapy and mechanical ventilation. These differences support the notion that increased MCV variability reflects broader physiological instability rather than an isolated hematologic change.

The observation that increased MCV variability was most pronounced in infectious and respiratory disease states supports the interpretation of MCV variation as a marker of systemic inflammatory and physiological stress rather than disease-specific hematologic pathology. This is consistent with previous reports in severe infections, including COVID-19, where dynamic changes in erythrocyte indices have been linked to disease severity.[9,15]

From a hematological perspective, short-term changes in mean corpuscular volume are unlikely to reflect true volumetric alterations of mature erythrocytes, which have a lifespan of approximately 120 days and do not actively change cell volume.[24] Instead, fluctuations in population-level MCV within a few days most likely arise from shifts in erythrocyte composition,[25] including the introduction of stored erythrocytes through transfusion, loss of specific cell populations due to bleeding, or stress-induced erythropoiesis with release of larger reticulocytes.[26] In this context, MCV variability should be interpreted as an indirect marker of acute hematological and systemic perturbations rather than intrinsic red cell remodeling. Although systematic reticulocyte data were not available in this real-world ICU cohort, the strong association with transfusion exposure and inflammatory severity supports this population-based interpretation.

Hsieh et al. (2017) suggest that changes in MCV among CKD patients may reflect erythropoietic stress and bone marrow response, which could similarly apply to ICU patients with renal involvement.[10] Additionally, Tang et al. (2025) reported that sepsis-induced inflammation significantly affects MCV, highlighting its potential as a biomarker for immune response and tissue damage in critically ill populations.[9] In line with this interpretation, the higher prevalence of chronic kidney disease observed in the low MCV-variation group (Table 1) likely reflects predominantly chronic and relatively stable erythropoietic alterations in CKD, rather than acute short-term variability of erythrocyte indices during critical illness.

Fluid balance shifts are another important driver of MCV variability. Hyperhydration during aggressive fluid resuscitation can lead to hemodilution, reducing red blood cell concentration and affecting MCV. Conversely, dehydration or fluid loss may cause hemoconcentration, resulting in an apparent increase in MCV values. These dynamic changes in intravascular volume are well-documented and could directly influence erythrocyte indices.[11,15]

Additionally, inflammation-driven disruptions in erythropoiesis may further contribute to MCV shifts. Pro-inflammatory cytokines such as IL-6 and TNF-α can alter red blood cell production and lifespan, causing variations in size and volume distribution.[15] This supports the hypothesis that MCV is a reflection of underlying pathophysiological instability in critically ill patients.

Subgroup analysis and clinical implications

Interestingly, our study did not reveal clear differences in outcomes across specific patient characteristics with respect to MCV variation. This absence of a clear stratification contrasts with findings from specific populations, such as cardiac patients and CKD patients.[10,11] This observation likely reflects the pronounced heterogeneity of a general ICU population, in which multiple overlapping pathophysiological processes coexist and may obscure disease-specific signals that are more readily detectable in selected cohorts.

To enhance the predictive accuracy and better identify high-risk subgroups, integrating MCV variability with additional prognostic markers may be beneficial. Specifically, Red Cell Distribution Width (RDW), C-Reactive Protein (CRP) and Procalcitonin (PCT) have been shown to have significant prognostic value in critically ill patients. These markers reflect systemic inflammation and hematological stress, which are often associated with worse outcomes in ICU settings.[21,22] Combining these parameters with MCV variability in a multi-marker model could improve the accuracy of risk stratification and reduce the rate of false-positive predictions. Although RDW is conceptually closely linked to MCV dynamics, systematic RDW data were not available for analysis in the present study. Furthermore, advanced machine learning techniques could be leveraged to identify non-linear interactions between these biomarkers and clinical outcomes, offering a more granular understanding of patient risk profiles (Lanspa et al., 2014). Such approaches have demonstrated success in improving prognostic models in ICU settings by capturing complex relationships in clinical data.

Future research perspectives

Future research should focus on prospectively characterizing MCV dynamics within a mechanistically informed framework. Specifically, studies integrating serial MCV measurements with reticulocyte counts and red cell distribution width (RDW) may help to disentangle true erythropoietic responses from population shifts driven by transfusion or fluid balance. In addition, controlled investigations examining short-term MCV changes in response to defined clinical interventions, such as erythrocyte transfusion or fluid resuscitation, could further clarify the physiological drivers of observed variability. Finally, incorporating longitudinal MCV trajectories into multivariable or machine-learning–based models alongside established dynamic biomarkers may improve the representation of systemic instability and enhance individualized risk stratification in critically ill patients.

Limitations

This study has limitations that need to be considered when interpreting the results. Its retrospective design introduces potential biases, including selection and information bias. Additionally, the analysis was conducted at a single center, which may limit external validity. Moreover, the reliance on electronic health records (EHR) for data extraction could result in inaccuracies due to missing or incomplete documentation. Importantly, variability estimates derived from a limited number of measurements are influenced by sampling frequency. Infrequent or irregular laboratory sampling may artefactually inflate apparent variability or fail to capture true underlying biological dynamics, a well-recognized limitation of EHR-based observational studies. Next, our variability metric treats increase and decreases in MCV symmetrically. While directional trends may convey additional mechanistic information, we deliberately focused on early overall variability as a robust prognostic marker. Directional analyses represent an important topic for future work. Also, preexisting hematologic disorders and severe nutritional deficiencies (e.g., vitamin B12 or folate deficiency) may lead to chronically abnormal or unstable MCV values independent of acute critical illness and thus represent potential sources of residual confounding. In addition, systematic data on red cell distribution width (RDW), a direct marker of erythrocyte size heterogeneity that complements the interpretation of MCV dynamics, were not available in the present dataset. Future studies should therefore investigate MCV variability in conjunction with RDW to provide a more comprehensive characterization of erythrocyte population dynamics in critical illness. Although such conditions were uncommon in our ICU cohort and exclusion of affected patients (n = 279) did not materially alter the results, we cannot fully exclude residual effects. Finally, while we identified associations between MCV variability and mortality, causality cannot be inferred from observational data.

Future prospective, multicenter studies are necessary to validate these findings and explore whether interventions targeting MCV stabilization could influence clinical outcomes in ICU settings.

Conclusion

In conclusion, our study highlights the strong concordance between early MCV variation and in-hospital mortality in critically ill patients, reflecting the close link between hematologic dynamics and overall physiological instability. While MCV variation is not an independent predictor after adjustment for established severity markers, it may serve as an easily accessible adjunctive indicator of disease severity and systemic stress. Future research should aim to validate these findings in multicenter cohorts and to explore how dynamic hematologic metrics can be integrated into longitudinal prediction frameworks for individualized risk assessment in the ICU setting.

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Consent to participate

Informed consent was not required due to the retrospective nature of the study.

Author contributions

Conceptualization, M.B., T.B and S.B.; data curation and formal analysis, S.B., M.B.; validation, all authors; visualization, S.B. and M.B. writing – original draft preparation, S.B., M.B. and T.B.; writing – review and editing, all authors. All authors have given final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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Declaration of conflicting interests

T.B. is an employee and shareholder of Roche Diagnostics International, Rotkreuz, Switzerland. All other authors declare that they do not have a conflict of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available. Data will be made available upon reasonable request to the corresponding author, subject to approval by the relevant institutional committees and in accordance with all applicable laws and regulations. Requests will be processed within 6–8 weeks. Data usage will be governed by a data use agreement that prohibits re-identification and limits usage to the approved scientific purpose. Source data for all main figures are provided as Supplementary Data in Excel format.

Code availability

The code used for data preprocessing, model training and evaluation will be made available upon reasonable request for academic, non-commercial use. Requests should be directed to the corresponding author and will be subject to approval by the relevant institutional committees and in accordance with all applicable laws and regulations. All code was written using R Statistical Software (v4.2.3)17.

Supplemental material

Supplemental material for this article is available online.

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