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Association of WPR with in-hospital mortality in patients with severe acute pancreatitis: a study based on the MIMIC-IV database

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Article

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Association of WPR with in-hospital mortality in patients with severe acute pancreatitis: a study based on the MIMIC-IV database

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Abstract

Background

Severe acute pancreatitis (SAP) is a common critical emergency in clinical practice and carries an extremely high risk of mortality. WPR (white blood cell to platelet ratio), as a potential clinical indicator, has an unclear prognostic value in SAP patients. This study aimed to investigate the association between WPR and the risk of in-hospital mortality in patients with SAP.

Methods

This was a retrospective observational study based on the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. After applying the inclusion and exclusion criteria, 902 patients with SAP were ultimately enrolled. The optimal cutoff value of WPR was determined to be 0.065 using the maxstat package, and patients were divided into high-WPR and low-WPR groups accordingly. Cox proportional hazards models were used to evaluate the independent association between WPR and in-hospital mortality, and the results were presented in three models (crude model; Model 1 adjusted for age; Model 2 further adjusted for pH, lactate, acute renal failure, and continuous renal replacement therapy [CRRT]). In addition, restricted cubic splines (RCS), Kaplan–Meier survival curves, subgroup analyses, and mediation analyses were performed.

Results

Among the 902 patients included, 774 were in the survivor group and 128 in the non-survivor group. Multivariable Cox regression (Model 2) showed that the high-WPR group had a significantly higher risk of in-hospital mortality than the low-WPR group (HR = 1.369, 95% CI: 1.048–1.788, P = 0.0212). RCS analysis demonstrated a significant association between WPR and mortality risk in SAP (P-overall = 0.001). The Kaplan–Meier survival curves showed that the high-WPR group had significantly lower survival (P = 0.00032). Mediation analysis revealed that lactate and creatinine mediated 10.58% and 11.15% of the association, respectively.

Conclusions

WPR is an independent risk factor for in-hospital mortality in patients with SAP. Clinical monitoring of WPR levels may facilitate early identification of high-risk patients.

Keywords: white blood cell to platelet ratio; severe acute pancreatitis; in-hospital mortality; MIMIC-IV database; lactate; creatinine.

Introduction

Acute pancreatitis (AP) is a common acute abdomen condition in clinical practice, with approximately 10%–20% of patients progressing to severe acute pancreatitis (SAP) [1]. As the critical subtype, SAP is pathologically characterized by pancreatic necrosis, systemic inflammatory response syndrome, and multiple organ failure. Despite continuous advances in intensive care support, the mortality of SAP has remained high over the past decades, ranging from 10% to 30% [2]. In recent years, the global incidence of SAP has been increasing, partly due to the rising prevalence of risk factors such as cholelithiasis, hyperlipidemia, and alcohol consumption, which has also led to substantial healthcare resource utilization and economic burden [3]. Moreover, because patients with SAP often require prolonged intensive care unit (ICU) admission for organ support, fluid resuscitation, and nutritional therapy, they impose urgent demands on ICU beds, medical equipment, and human resources, thereby placing a heavy burden on the intensive care system [4].

In this context, scoring systems such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) are widely used for severity assessment and prognosis prediction in critically ill patients, but their clinical application has certain limitations. On the one hand, these scoring systems typically incorporate multiple physiological, biochemical, and clinical variables, making the calculation cumbersome and time-consuming, and thus difficult to perform rapidly in clinical practice, which limits their immediate use in emergency settings [5]. On the other hand, although these systems can effectively discriminate mortality risk at the population level, they reduce patients to standardized parameters and neglect inter-individual differences, and their predictive performance may vary across different disease spectra [6]. Therefore, there is an urgent clinical need to explore novel biomarkers or composite indicators that are rapid, simple, and capable of individualized risk stratification, in order to compensate for the shortcomings of existing scoring systems and to guide clinical decision-making and therapeutic strategies.

Platelets and white blood cells are core effector cells in the inflammatory response and immune regulation, and their quantitative changes and functional interactions play critical roles in the development and progression of various diseases. An elevated white blood cell count is considered a marker of acute inflammation and is associated with adverse outcomes in multiple critical illnesses [7]. Platelets not only participate in thrombosis but also release inflammatory mediators upon activation that can modulate immune cell functions [8]. Traditionally, these indicators have been used separately for prognostic assessment; for example, white blood cell count can predict 90-day mortality in patients with intracranial hemorrhage [7]. However, emerging evidence suggests that combined assessment of multiple blood cell parameters may provide better predictive performance. For instance, in patients with acute ischemic stroke, the combination of high white blood cell count and low platelet count at admission was superior to either parameter alone in predicting in-hospital mortality [9]. Furthermore, composite indices integrating white blood cell and platelet parameters, such as the white blood cell count-to-mean platelet volume ratio (WMR), have been confirmed to be independently associated with poor 3-month functional outcomes in patients with acute ischemic stroke [10]. Of note, although studies have investigated the value of other composite indicators, such as the platelet-to-lymphocyte ratio (PLR), in diseases including idiopathic pulmonary fibrosis [11], systematic evidence is still lacking regarding the prognostic value of

the white blood cell count-to-platelet count ratio (i.e., white blood cell-to-platelet ratio, WPR) in patients with SAP.

Further studies have demonstrated that platelet-related indicators, such as platelet count and the platelet-to-lymphocyte ratio (PLR), have prognostic value in various inflammatory diseases, including sepsis [12]. Specifically, an elevated PLR is independently associated with increased long-term mortality and can serve as a predictor of poor prognosis in patients with acute coronary syndrome [12]. In addition, the platelet distribution width-to-lymphocyte ratio (PDWLR) has shown potential as a prognostic marker in the severity assessment of snakebite envenomation [13]. However, although systemic inflammation plays a central role in the pathogenesis of SAP, and previous studies have explored the value of the neutrophil-to-lymphocyte ratio (NLR) and PLR in predicting the severity of acute pancreatitis [14], the specific predictive performance of the platelet distribution width-to-lymphocyte ratio (PDWLR), a composite index combining platelet distribution width and lymphocyte count, in patients with SAP has not yet been clarified.

Although the value of various biomarkers in the prognostic assessment of SAP has been demonstrated in previous studies, an integrated indicator that is readily accessible, low-cost, and capable of effectively predicting in-hospital mortality is still lacking in clinical practice. White blood cell count and platelet count are routine laboratory tests that reflect the degree of inflammatory response and coagulation status, respectively. However, existing studies have mostly focused on the prognostic value of a single indicator, and studies constructing novel composite indicators combining these two parameters, such as WPR, to assess the prognosis of SAP remain scarce. Therefore, this study aimed to utilize large-sample data of patients with SAP from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to investigate the association between WPR and the risk of in-hospital mortality in patients with SAP.

Materials and Methods

Data sources

This study was a retrospective observational study based on the Medical Information Mart for Intensive Care IV (MIMIC-IV) version 3.1 database and the eICU Collaborative Research Database (eICU-CRD), both provided by the PhysioNet platform. MIMIC-IV is a freely accessible database containing de-identified electronic health records of patients admitted to the Beth Israel Deaconess Medical Center between 2008 and 2019 [15]. The database encompasses comprehensive demographic characteristics, physiological monitoring parameters, laboratory results, and disease diagnoses based on the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10). All personally identifiable information has been de-identified to protect patient privacy; therefore, informed consent and approval from the Institutional Review Board were not required for this study. One of the authors (S.-X.Z.) obtained access to the MIMIC-IV database (record ID: zsx2262521784) after completing the web-based training course and passing the “Protecting Human Research Participants” examination. This study was conducted in strict accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [16].

Study population

A total of 923 patients with severe acute pancreatitis were identified from the MIMIC database. The exclusion criteria were as follows: (1) missing key data (e.g., WPR) and extreme values. Ultimately, 902 patients were enrolled, including 128 patients with in-hospital death and 774 survivors (Figure 1).

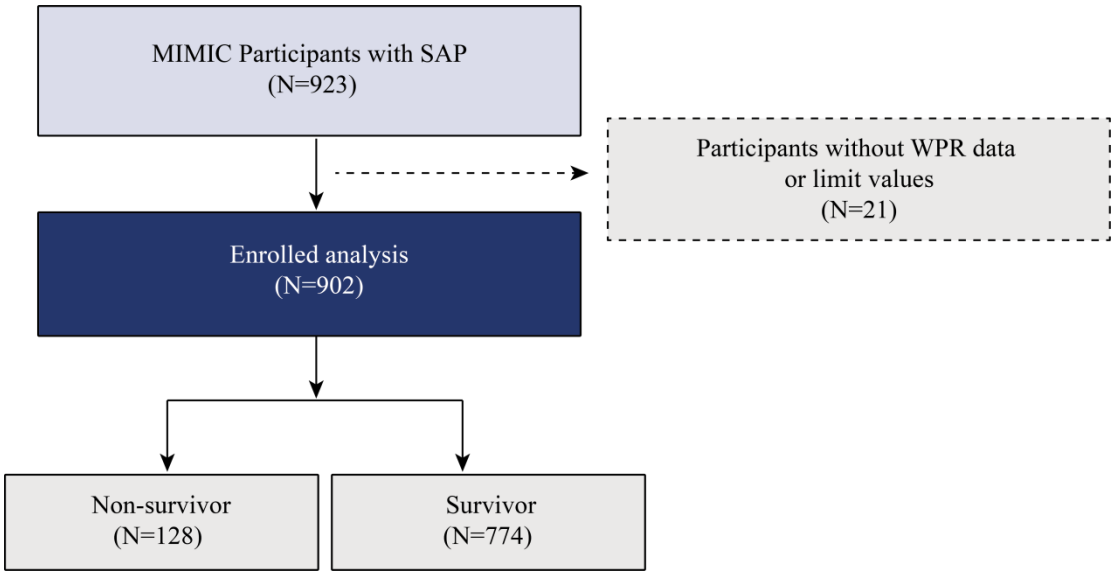


Figure 1. Flowchart of the sample selection from the MIMIC

WPR indicator

The white blood cell-to-platelet ratio (WPR) is increasingly recognized as an important biomarker in various diseases, including cardiovascular disease. WPR reflects the balance between pro-inflammatory and anti-inflammatory leukocytes, which is critical for maintaining immune homeostasis and responding to stressors such as infection or tissue injury. In addition to their role in hemostasis, platelets are key mediators of inflammation through the release of cytokines and interactions with immune cells, and their incorporation into biomarker ratios such as WPR is therefore of particular significance in critical illness [17].

Severe acute pancreatitis

Data extraction was performed using Structured Query Language (SQL) in a PostgreSQL environment (version 14.6). Patients diagnosed with AP were identified using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes, specifically 5770, K8590, K8510, K8520, K859, K8580, K859, K851, K8521, K8522, K852, K8500, K8592, K8511, K8530, K8581, K8522, K8512, K853, K8582, K8501, K8502, K8502, and K8531 in the MIMIC-IV database.

Ascertainment of mortality outcome and follow-up

The primary outcome of this study was in-hospital mortality. Survival status was defined as the final clinical outcome during hospitalization. Follow-up time was defined as the duration from hospital admission until the occurrence of death or discharge. For patients discharged during the follow-up period, the survival status was recorded as alive, and the discharge time was used as the right-censoring time point. Length of hospital stay was calculated in days. All outcome data were extracted from the core record tables of the MIMIC database.

Covariate assessment and multicollinearity analysis

Potential confounders, including demographic characteristics, vital signs, laboratory

indicators, and comorbidities, were extracted to evaluate their associations with SAP severity scores (GCS, OASSAP, SOFA, APS III, SAPS II, CHARLSON) and clinical interventions such as mechanical ventilation and continuous renal replacement therapy (CRRT). To ensure the stability of the multivariable model, univariate Cox regression analysis was first performed on the above variables (Table S2). The results showed that age, blood pressure indices (NBPS/D/M), body temperature, white blood cell count (WBC), lactate, pH, severity scores (SOFA, OASSAP, APS III, etc.), acute renal failure, and CRRT were significantly associated with in-hospital mortality in SAP patients ($P < 0.05$). Subsequently, variables with $P < 0.05$ in the univariate analysis were subjected to variance inflation factor (VIF) analysis (Table S3). All included variables had VIF values strictly less than 4, with the maximum being the SOFA score (VIF = 3.546). Other important covariates, such as age (VIF = 2.036) and WPR (VIF = 1.468), also exhibited low VIF values. These results indicated that there was no serious multicollinearity among the covariates included in the model. Finally, based on clinical prognostic significance and statistical significance, the covariates adjusted in the multivariable model (Model 2) were age, pH, lactate, acute renal failure, and CRRT.

Statistical analysis

As there is currently no consensus on the threshold for excluding variables with missing values, a 40% missingness threshold was set in this study. Before each model fitting, data were assumed to be missing at random (MAR), and multiple imputation was performed using the mice package in R. The distributions of variables were consistent before and after multiple imputation ($P > 0.05$), indicating reliable imputation results. The optimal cutoff value of WPR was determined using the maxstat package based on maximally selected rank statistics, and patients were divided into low-WPR and high-WPR groups. To explore the potential nonlinear relationship between WPR and in-hospital mortality in SAP patients, restricted cubic spline (RCS) analysis was used to evaluate the dose–response relationship between WPR and mortality by plotting predicted risk curves. Cox proportional hazards models were used to evaluate the independent association between WPR and in-hospital mortality risk in SAP patients, and the results were presented in three models: the crude model (unadjusted), Model 1 (adjusted for age), and Model 2 (further adjusted for pH, lactate, acute renal failure, and CRRT). Kaplan–Meier curves were used to compare survival probabilities among SAP patients with different WPR levels, with between-group differences assessed by the log-rank test. To further explore the potential pathways through which WPR affects the prognosis of SAP patients, mediation analysis was performed to evaluate the mediating effects of laboratory indicators on the association between WPR and in-hospital mortality. The total effect, direct effect, indirect effect, and proportion mediated were calculated. Subgroup and interaction analyses were conducted according to age, sex, race, language, marital status, and relevant comorbidities, and the results were displayed using forest plots. All analyses were performed using R software, and $P < 0.05$ was considered statistically significant [18].

Results

Baseline characteristics of the study population

A total of 902 patients with severe acute pancreatitis (SAP) were identified from the MIMIC-IV database according to the inclusion and exclusion criteria, including 128 non-survivors and 774 survivors (Table 1). Missing data were imputed using multiple

imputation, and the distributions of all variables were consistent before and after imputation (Table S1). The optimal cutoff value of WPR was determined to be 0.065. Accordingly, patients were divided into two groups: the high-WPR group (WPR ≥ 0.065, N = 448) and the low-WPR group (WPR < 0.065, N = 454) (Table 2-M, Figure S1-M). Compared with the low-WPR group, the high-WPR group had significantly higher levels of white blood cell count (WBC), anion gap, lactate, total bilirubin, liver enzymes (ALT and AST), blood urea nitrogen, and creatinine (all P < 0.001).

Association between WPR and in-hospital mortality in patients with severe acute pancreatitis

Cox regression analysis

Weighted Cox regression analysis showed that WPR was positively associated with in-hospital mortality in patients with SAP in the MIMIC database. In the unadjusted crude model, patients in the high-WPR group (WPR ≥ 0.065) had a significantly increased risk of in-hospital mortality compared with those in the low-WPR group (WPR < 0.065) (crude model: HR = 1.601, 95% CI: 1.233–2.079, P < 0.0001). This association remained stable in Model 1 (HR = 1.556, 95% CI: 1.198–2.022, P < 0.0001) and Model 2 (HR = 1.369, 95% CI: 1.048–1.788, P = 0.0212) (Table 3).

Restricted cubic spline (RCS) analysis

RCS analysis demonstrated a positive association between WPR and in-hospital mortality in patients with SAP, with the mortality risk increasing significantly as WPR increased. In the MIMIC database, the overall trend was significant in all models (crude model: P for overall = 0.001; Model 1: P for overall = 0.001; Model 2: P for overall = 0.001), whereas the nonlinearity was not significant in any model (crude model: P for nonlinearity = 0.08; Model 1: P for nonlinearity = 0.149; Model 2: P for nonlinearity = 0.24) (Figure 2a–c).

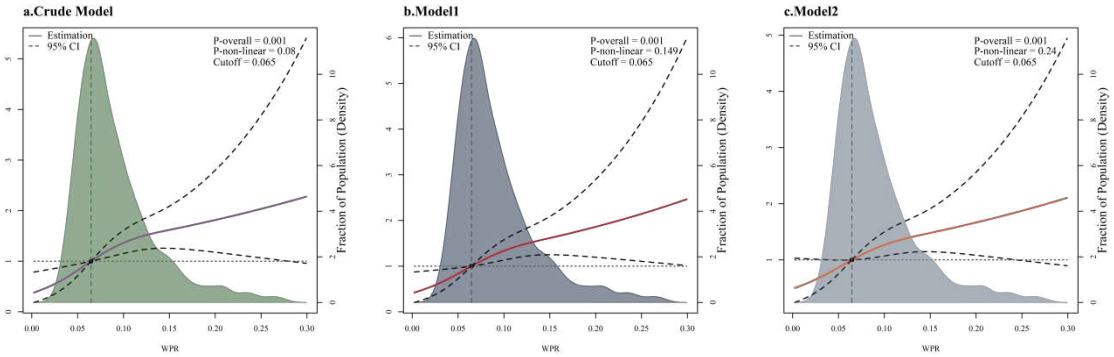


Figure 2. RCS Analysis of the Association Between WPR and Mortality in SAP

Survival curve analysis

Kaplan–Meier survival curve analysis showed that, in evaluating the association between WPR and in-hospital mortality in patients with SAP, the high-WPR group had a lower survival probability at the early stage of follow-up, with a more rapid decline over time, indicating a higher risk of death within a given period. In contrast, the low-WPR group exhibited a higher survival probability and a slower decline in the survival curve, suggesting a better survival rate during the follow-up period. The difference in survival between the high- and low-WPR groups was statistically significant (MIMIC database: P = 0.00032) (Figure 3).

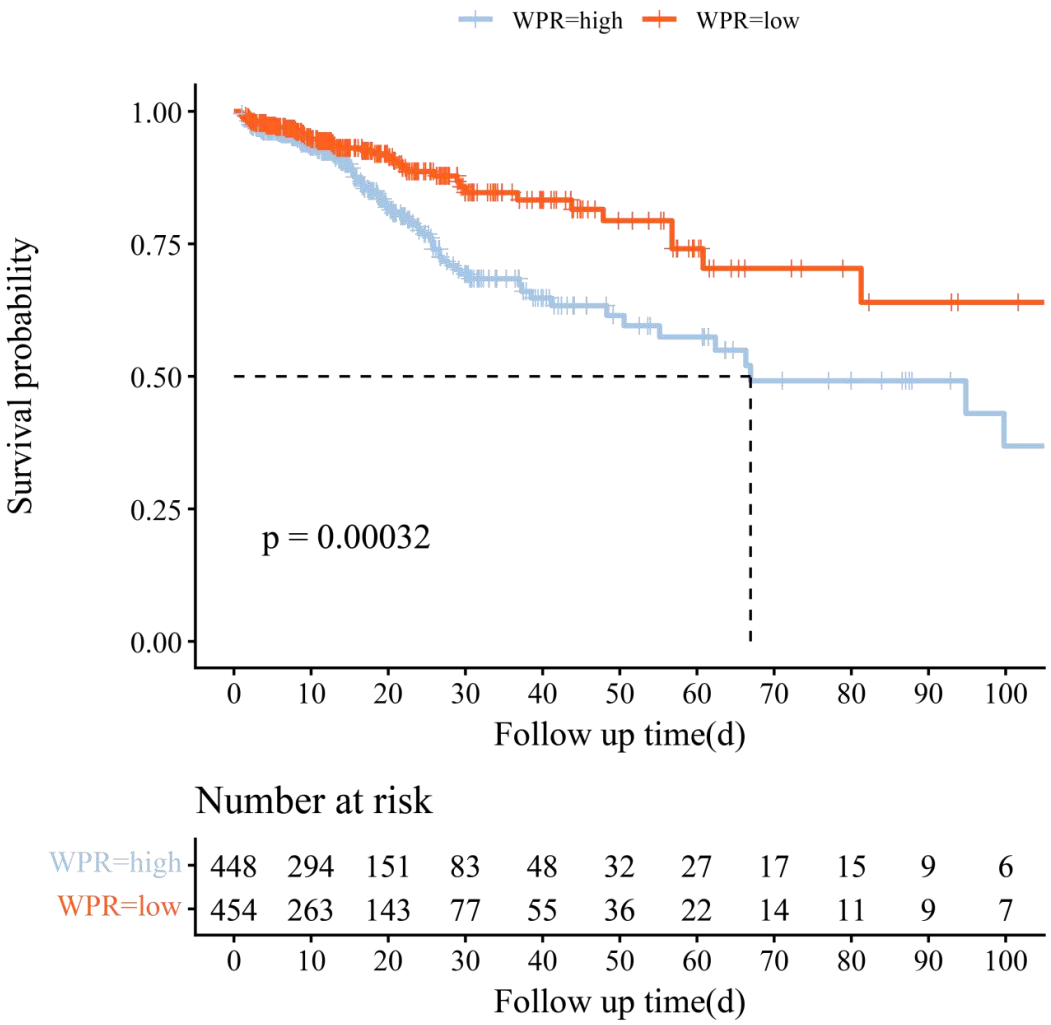


Figure 3. Kaplan – Meier curves of the survival rate with higher and lower WPR

Subgroup analysis

In the MIMIC database, subgroup analyses were performed according to age, sex, and relevant comorbidities to investigate the association between WPR and in-hospital mortality in patients with severe acute pancreatitis (SAP). WPR was found to be a consistent risk factor for in-hospital mortality across different subgroups. No significant interaction effects were observed in any subgroup except for COPD (P for interaction = 0.004), whereas all other subgroups showed P for interaction > 0.05, indicating that the prognostic value of WPR was relatively stable across different patient populations. Detailed results are presented in Figure 4.

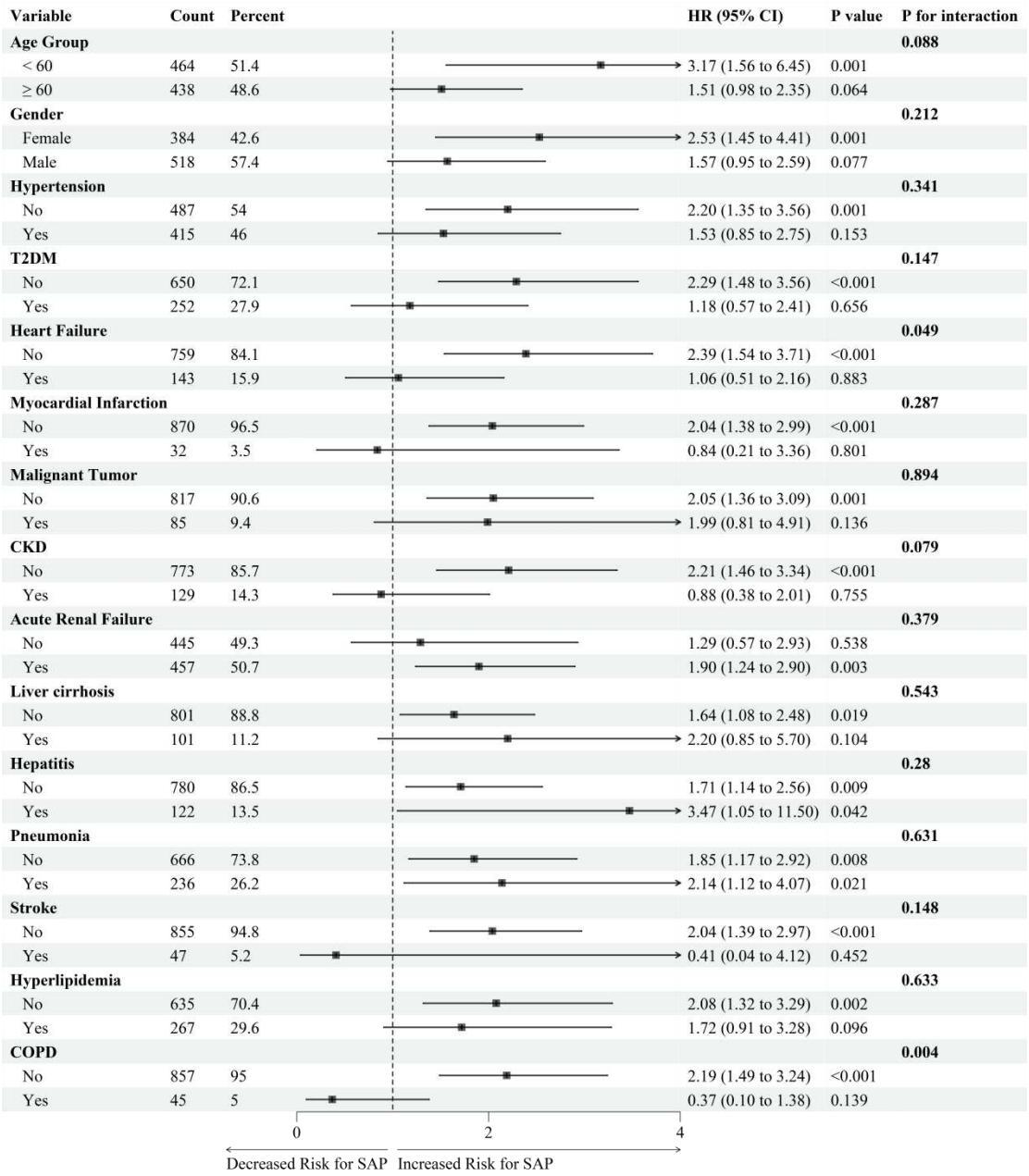


Figure 4. Subgroup analyses of the relationship between WPR Score and SAP.WPR Score was analyzed as a continuous variable

Mediation analysis

Mediation analyses were performed to investigate the mediating effects of lactate and creatinine on the association between WPR and in-hospital mortality in patients with SAP.

In the MIMIC cohort, lactate mediated 10.58% (95% CI: 3.38%–23.73%) of the association. Specifically, elevated WPR significantly increased lactate levels (Path a: β = 3.189, P = 0.0189), which in turn significantly increased the risk of death (Path b: β = 0.185, P < 0.001). After controlling for the mediator, the direct effect of WPR on mortality remained significant (direct effect HR = 201.654, P < 0.001) (Table S4, Table S5, Figure 5a).

Similarly, creatinine mediated 11.15% (95% CI: 3.69%–29.43%) of the association. Specifically, elevated WPR significantly increased creatinine levels (Path a: β = 4.684, P <

0.001), which in turn significantly increased the risk of death (Path b: β = 0.133, P < 0.001). After controlling for the mediator, the direct effect of WPR on mortality remained significant (direct effect HR = 125.437, P < 0.001) (Table S4, Table S5, Figure 5b).

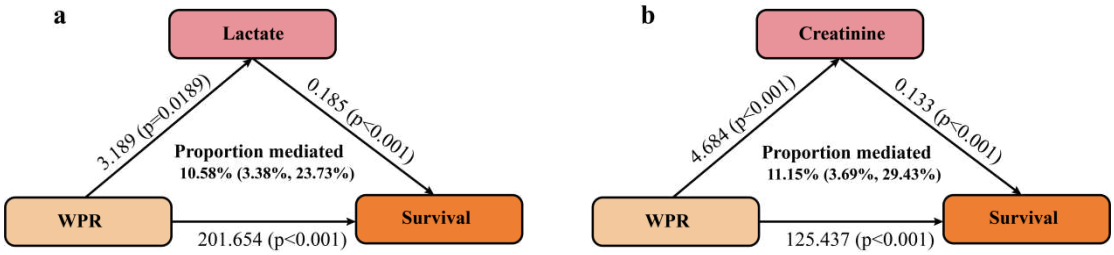


Figure 5. The mediating effect between WPR and survival

Box plot analysis

The distribution of WPR between survivors and non-survivors among patients with severe acute pancreatitis (SAP) was compared in the MIMIC dataset (Figure 6). The results demonstrated a statistically significant difference in WPR between the survival and non-survival groups (P < 0.0001). The box plot showed that the median WPR in the non-survivor group was markedly higher than that in the survivor group, further supporting the role of WPR as a potential risk factor for poor prognosis in patients with SAP.

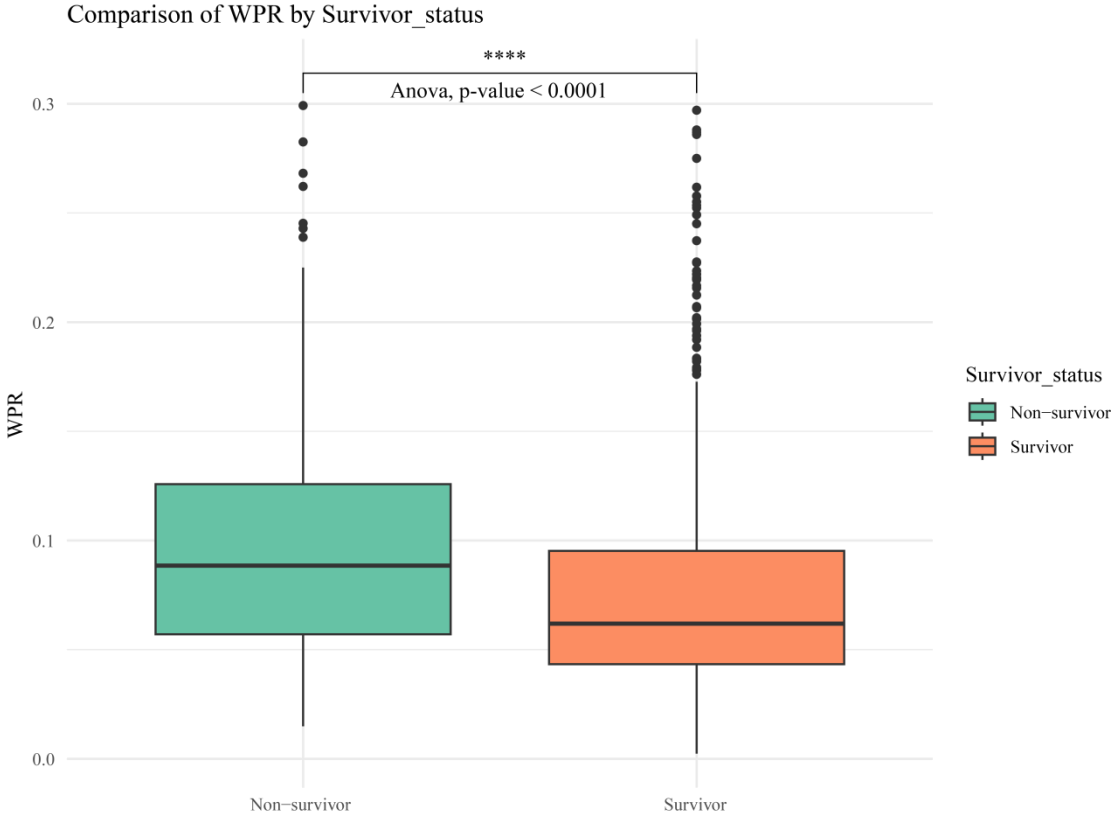


Figure 6. boxplot_WPR_Survivor_status_with_pairwise_p_value

Discussion

The present study, based on an analysis of the large intensive care database MIMIC-IV, demonstrated that the white blood cell-to-platelet ratio (WPR) is an independent risk factor for in-hospital mortality in patients with severe acute pancreatitis (SAP). Previous studies

have extensively explored the role of various routine blood cell-based inflammatory indicators in predicting the severity and prognosis of acute pancreatitis (AP). For example, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been shown to correlate with AP severity and to exhibit certain value in predicting severe disease and adverse outcomes [19]. In addition, the red blood cell distribution width-to-platelet ratio (RPR) has also been proposed as a simple prognostic marker for assessing AP severity and mortality risk [20]. However, most studies have focused on the efficacy of a single indicator or on predictive models combining multiple parameters, such as inflammation-based models or low-grade inflammation scores. Although these studies have highlighted the central role of the inflammatory response in AP progression [21], the prognostic value of WPR—a ratio integrating white blood cells and platelets, which represent the two key cellular components of the inflammatory and coagulation systems, respectively—has not been systematically evaluated in patients with SAP using a large clinical database. The present study fills this gap by demonstrating, for the first time, that elevated WPR is an independent risk factor for mortality in SAP. Of note, the role of platelet-related parameters in AP has received increasing attention. Previous studies have found that a decreased platelet count is associated with disease severity and organ failure [22]. In the present study, WPR integrates the dynamic balance between these two cell types, and our findings are consistent with the theory that thrombocytopenia and leukocytosis jointly participate in the pathophysiological processes of SAP.

In this context, the present study further suggests that WPR, as a composite parameter integrating leukocyte and platelet counts, may have superior predictive value compared with traditional single inflammatory or coagulation indicators. Previous studies have established that thrombocytopenia and excessive inflammation are intertwined in the pathological progression of SAP, collectively promoting microcirculatory disturbance and organ injury. As core pro-inflammatory effector cells, elevated leukocyte levels are positively correlated with the extent of pancreatic necrosis, whereas a reduced platelet count reflects activation and consumption of the coagulation system. By combining these two dimensions, WPR captures the synergistic pathological effects between inflammation and coagulation. It has been proposed that, in critical conditions such as septic shock, dynamic changes in leukocyte–platelet composite parameters are more predictive of adverse outcomes than single indicators. The present results are consistent with this notion, suggesting that WPR may identify high-risk patients at an early stage of SAP, thereby facilitating more intensive monitoring or early intervention in clinical practice. Furthermore, given that patients with SAP are at risk of systemic inflammatory response syndrome and disseminated intravascular coagulation, the composite signal reflected by WPR may herald a prognostic deterioration window earlier than individual parameters. Therefore, as a readily available composite index, WPR holds promise as a bedside early-warning tool in clinical practice, particularly in resource-limited ICU settings.

Compared with previous studies focusing on the value of single inflammatory biomarkers, such as white blood cell count or platelet count, in predicting AP severity, the WPR proposed in the present study is intended to capture the dynamic balance between leukocytes and platelets during SAP progression. For instance, although NLR and PLR have some value in predicting SAP, a single indicator is often insufficient to fully reflect the

complex pathophysiological processes of SAP. The core pathological mechanisms of SAP involve the synergistic deterioration of the inflammatory storm and microcirculatory disturbance, and leukocytes and platelets serve as key effector cells in these two systems, respectively; their interaction may thus be of greater clinical significance than either parameter alone. A previous study reported that the platelet-to-white blood cell ratio (PWR) has independent prognostic value in patients with acute-on-chronic liver failure [23], as this ratio integrates the quantitative relationship between platelets and leukocytes and reflects the interaction between inflammation and coagulation. In addition, some investigators found that composite models combining multiple inflammatory indicators, such as a model based on platelets, C-reactive protein, and lymphocytes, were superior to single indicators in diagnosing SAP. Another study in acute myeloid leukemia also confirmed that PWR, as a parameter integrating platelet and leukocyte information, had prognostic predictive ability comparable to that of established molecular markers [24]. Consistent with these findings, WPR in the present study may more comprehensively reflect the interaction between systemic inflammation and microcirculatory disturbance in SAP, a synergistic effect that plays an important role in driving disease progression toward a severe state. Therefore, exploring the association between WPR and the prognosis of SAP patients may provide a more integrated and convenient biological indicator for early risk stratification.

Compared with traditional clinical scoring systems, WPR is a bedside indicator calculated from routine blood cell counts, requiring no additional cost or specialized equipment, and thus has significant clinical practicality and generalizability. Previous studies have confirmed that WPR exhibits independent and reliable predictive value for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage and for 28-day all-cause mortality in patients with cardiac arrest. Furthermore, a negative correlation between WPR and left atrial appendage emptying velocity has been reported in patients with non-valvular atrial fibrillation, suggesting that WPR may serve as a simple indicator for assessing thrombotic risk [25]. In the assessment of intracranial aneurysm stability, WPR, as a component of the systemic immune-inflammation index, was significantly associated with unstable aneurysm progression [26]. Similarly, perioperative WPR demonstrated good predictive performance for bacteremia in patients with severe burns [27]. Collectively, evidence from these different critical care settings indicates that WPR, as a composite inflammatory indicator integrating leukocyte and platelet information, reflects an immune–coagulation interaction disorder that is common to the prognosis of various diseases. Therefore, compared with conventional scoring systems that require cumbersome multi-parameter calculation, WPR is easier to obtain rapidly and monitor dynamically in clinical practice, and possesses superior potential for point-of-care application.

This study included 902 patients with SAP from the MIMIC-IV database, representing a relatively large sample size. Previous MIMIC-IV-based studies on SAP have mostly enrolled several hundred to over a thousand patients. For example, one study including 1,341 patients investigated the association between early anticoagulation therapy and in-hospital mortality in SAP [28], and another study including 1,032 patients developed a risk prediction model for septic shock in SAP [29]. In comparison, the sample size of the present study (902 patients) falls within the common range of similar studies, providing adequate statistical power for the analyses. In addition, a multivariable adjustment strategy was adopted in the Cox proportional

hazards models to control for potential confounders. In previous prognostic studies of SAP, such as a MIMIC-IV-based study investigating the glucose-to-lymphocyte ratio (GLR), multivariable Cox regression was also used to adjust for key variables including age and the SOFA score [30]. Similarly, another study examining the blood urea nitrogen-to-albumin ratio (BAR) for predicting mortality in AP employed a multivariable-adjusted Cox regression model [31]. These studies all underscore the importance of controlling for confounders in multivariable models to evaluate independent prognostic value. Furthermore, the present study applied restricted cubic spline (RCS) analysis to explore the potential nonlinear relationship between WPR and mortality risk in SAP. RCS has been widely used in recent critical care research. For example, one study used RCS to analyze the dose–response relationship between the albumin-corrected anion gap (ACAG) and mortality in AP and identified a nonlinear association [32]. Another study of cumulative serum creatinine exposure in SAP also employed RCS and revealed a nonlinear relationship between cumulative creatinine values and mortality, along with a threshold effect [33]. This flexible analytical approach helps more accurately characterize the complex association between the exposure variable and the outcome, thereby enhancing the reliability of the study conclusions. Taken together, the sample size, multivariable adjustment strategy, and RCS analysis in the present study constitute a relatively robust study design and provide a solid analytical foundation for examining the relationship between WPR and in-hospital mortality risk in SAP.

To further explore the potential biological pathways through which elevated WPR increases the risk of in-hospital mortality in SAP, the present study performed mediation analyses and identified lactate and creatinine as important mediators. Previous studies have established that microcirculatory disturbance is a central pathophysiological process in severe acute pancreatitis, leading to insufficient tissue perfusion and oxygen debt, which in turn results in lactic acidosis. Elevated lactate levels have been widely recognized as a key marker of organ dysfunction and adverse prognosis. Meanwhile, renal injury, as a common complication of SAP, is reflected by elevated creatinine levels. Creatinine is not only a classic indicator of the glomerular filtration rate, but its accumulation also reflects systemic injury mediated by impaired renal clearance capacity. Our findings suggest, at the epidemiological level, that the adverse effect of WPR on prognosis may be partially mediated by two pathways: aggravation of microcirculatory disturbance (marked by lactate) and impairment of renal function (marked by creatinine). This result is consistent with previous evidence on the interaction between microcirculatory disturbance and renal injury in critical illness. For example, in patients with sepsis or heart failure, reduced renal perfusion and metabolic disturbance often jointly contribute to adverse outcomes [34]. In summary, the present mediation analysis provides important epidemiological clues for future research, suggesting that improving microcirculatory disturbance and preserving renal function may be potential intervention targets for reducing mortality risk in high-risk SAP patients.

As a retrospective observational study, the present analysis is subject to inherent limitations. Although multivariable Cox regression was used to adjust for known confounders and RCS analysis was applied to explore potential nonlinear associations, the retrospective design cannot fully exclude the effects of unmeasured confounders, particularly key clinical variables such as anticoagulation strategy and the timing of source control. Previous studies

have clearly demonstrated that the timeliness and effectiveness of source control are decisive factors influencing the prognosis of patients with intra-abdominal infection and sepsis, with an impact that may even surpass the appropriateness of empirical antimicrobial therapy. Specifically, compared with delayed source control, immediate (<2 hours) or urgent (2–6 hours) source control interventions were significantly associated with lower mortality. Moreover, failure of source control, usually manifested as persistent inflammation, is a strong predictor of increased mortality risk [35]. In specific settings such as intra-abdominal candidiasis, the absence of adequate source control is associated with mortality rates exceeding 60%, which cannot be reversed even with appropriate antifungal therapy [36]. Recent studies in patients with septic shock have also confirmed that source control is an independent protective factor against mortality. Meanwhile, the use of anticoagulant therapy varies considerably among critically ill patients and may be associated with their prognosis. Therefore, these clinical variables, which were not captured in the database used in the present study, may exert confounding effects on our results. To overcome these limitations and more precisely validate the independent causal relationship between WPR and the prognosis of patients with SAP, future studies should be designed as prospective cohort studies that systematically incorporate key confounders—including the timing of source control, details of anticoagulation therapy, and dynamic severity scores—at the data collection stage, so as to provide a higher level of evidence-based medical evidence.

Based on the present findings, future research should focus on dynamically monitoring the trends of WPR changes and their interaction with treatment response in patients with SAP. Existing evidence suggests that WPR, as a composite indicator of the leukocyte-to-platelet ratio, may sensitively capture fluctuations in inflammatory status and immune function during the disease course of SAP, thereby providing real-time guidance for individualized fluid resuscitation and anticoagulation strategies. Therefore, future studies should not only validate the association between the rate of WPR change and clinical prognosis, but also investigate whether different patterns of WPR changes interact with patient responses to interventions such as fluid resuscitation and anticoagulation therapy. For example, high WPR variability or persistent elevation may indicate the need for more aggressive anti-inflammatory therapy or more refined volume management, whereas a stable low WPR may correspond to a relatively stable pathophysiological process. Elucidating such interactions will help transform WPR from a static risk-stratification indicator into a dynamic biomarker capable of guiding therapeutic decisions, thereby advancing the development of precision treatment strategies for SAP.

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Supplementary Materials

Author Contributions

D-L.L,D-X.X, S-X Z and W-L H. contributed equally to this work. All authors contributed to the study conception and design. Data collection and processing were performed by S-X Z and Z.C. Data analysis and visualization were performed by J-Y.L,X-H.C, F.Land G-B.Z. The first draft of the manuscript was written by D-L.L. and D-X.X; D-L.L, W-L.H, Z.C. conceptualized and critically revised the manuscript for important intellectual content, and is

the corresponding author responsible for final approval and submission. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The analyzed data in this retrospective study were from the Medical Information Mart for Intensive Care (MIMIC)-IV database upon recruitment between 2008 and 2019. Shao-Xiong Zheng has access to the database and was responsible for the data extraction. All participants were recruited from the ICU of the Beth Israel Deaconess Medical Center. The original data collection and de-identification process were approved by the Institutional Review Boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology. For this type of study, Ethical review and approval were waived.

Informed Consent Statement

The Institutional Review Board of the Beth Israel Deaconess Medical Center has given its approval for this database (2001P001699/14). All personal identifiers have been removed and instead replaced with randomly assigned numbers. As a result, the requirement for informed consent has been waived.

Data Availability Statement

The data analyzed in this study was obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database(https://physionet.org/, https://doi.org/10.13026/kpb9-mt58, accessed on 11 June 2025). To access the dataset, users must be credentialed, complete the required training (CITI Data or Specimens Only Research) and sign the data use agreement for the project.

Conflicts of Interest

The authors declare that they have no competing interests.

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