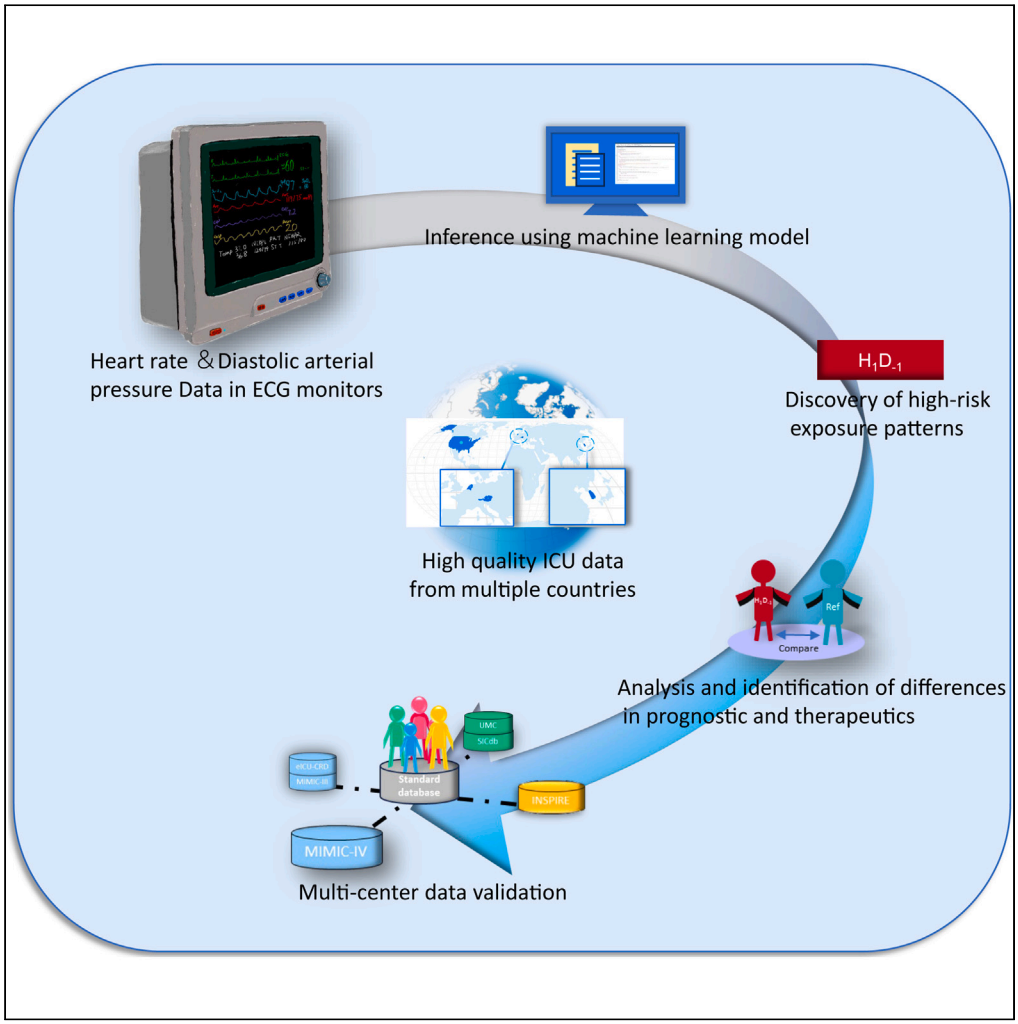
iScience

CellPress
OPEN ACCESS

Article

A novel vital sign pattern predicts sepsis-related myocardial injury mortality



Wanjun Liu, Jinjin Dai, Pengyue Zhang, Menglin Ni, Yafei Zhang, Haoshu Fang, Zhenhua Zhang

fanghaoshu@ahmu.edu.cn (H.F.)
zzh1974cn@163.com (Z.Z.)

Highlights

Early assessment of sepsis-associated myocardial injury is still lacking

The H_1D_{-1} exposure pattern is a high-risk exposure pattern

Validation across methodologies confirming its consistency and robustness

Liu et al., iScience *27*, 110787
September 20, 2024 Published by Elsevier Inc.
https://doi.org/10.1016/j.isci.2024.110787

iScience

CellPress
OPEN ACCESS

Article

A novel vital sign pattern predicts sepsis-related myocardial injury mortality

Wanjun Liu,[1,3] Jinjin Dai,[1,3] Pengyue Zhang,[1,3] Menglin Ni,[1] Yafei Zhang,[1] Haoshu Fang,[2,*] and Zhenhua Zhang[1,4,*]

SUMMARY

Non-invasive, real-time monitorable indicators for early assessment of sepsis-associated myocardial injury (SMI) are still lacking. We aimed to develop non-invasive, real-time indicators for early assessment of SMI using bedside heart rate (HR) and diastolic arterial pressure (DAP) monitors. In this multi-center cohort study, piece-wise exponential additive mixed models were used to estimate the exposure window and time fraction of the hazardous exposure proportion, and secondarily to analyze the exposure characterization on this basis to identify high-risk exposure pattern. In total, 20,043 patients were finally included; we found that SMI patients had the highest survival rate when HR was <90 bpm or DAP was between 50 and 70 mmHg. Further investigation revealed that the SMI high-risk exposure pattern was the H_1D_{-1} (HR $\geq$ 90 bpm and DAP $\leq$ 50 mmHg, exposure proportion > 0.3 and 0.2, respectively, and exposure window on admission day 1). H_1D_{-1} exposure pattern using glucocorticoids significantly increased the risk of mortality in H_1D_{-1}. Validation against various methodologies and data sources demonstrated acceptable consistency.

INTRODUCTION

The initial resuscitation strategy for sepsis is invaluable, but the additional cardiac loads of resuscitation have historically received inadequate attention.[1] The early identification of sepsis-associated myocardial injury (SMI) poses a considerable challenge,[2] yet its unmitigated progression can significantly compromise tissue perfusion, thereby exerting a pronounced impact on prognosis and elevating mortality rates.[3] While troponins and brain natriuretic peptide stand as sensitive markers for diagnosing myocardial infarction, their invasiveness and protracted analysis duration limit their expediency as blood markers.[4] Regrettably, non-invasive and dynamically oriented indices for the early assessment of SMI remain elusive, thereby potentially constraining the effectiveness of therapeutic interventions within this patient cohort. Consequently, we are currently undertaking an exploratory investigation to delineate a monitoring indicator characterized by dynamic scalability, with the overarching goal of enhancing patient survivability in the context of SMI.

In the intensive care unit (ICU), emphasis is placed on continuous real-time monitoring at the bedside, with a specific focus on heart rate (HR) and diastolic arterial pressure (DAP) as fundamental physiological parameters. HR is commonly utilized as a rudimentary proxy for assessing myocardial perfusion,[5] while DAP serves as an essential metric for gauging peripheral vascular resistance.[6] In clinical practice, rapid HR compensation can improve peripheral perfusion but increase pulsation and shorten cardiac diastolic period, causing increased myocardial oxygen consumption and decreased coronary blood supply.[2] Simultaneously, fluctuations in arterial pressure prompt cardiac compensation through adjustments in sympathetic nerve activity. Concurrently, variations in the cardiac cycle exert a direct impact on the level of diastolic blood pressure.[7] During the initial phase of shock, a decrease in systolic arterial pressure typically signifies insufficient cardiac output or an inadequate early blood volume. However, alterations in DAP are often modest during this period.[8] Persistently, the distributive shock seen in septic patients generally results from abnormal peripheral blood flow distribution and the failure of peripheral vasoconstriction.[9] Nevertheless, an overly aggressive approach to fluid resuscitation may worsen myocardial injury and intensify the strain on the cardiac pump. Under such circumstances, alterations in DAP emerge as superior markers for achieving a balance between peripheral perfusion and cardiac workload. Consequently, HR and diastolic blood pressure stand as invaluable indicators, offering critical insights into the management and prognosis of patients with SMI.

In summary, HR and DAP, as accessible yet dynamic indices within critical care, hold significant potential to impact mortality in individuals contending with SMI. Aligned with the rapid evolution of precision medicine and data science, our primary objective is to investigate an effective and responsive real-time measurement mechanism. This involves harnessing bedside HR and DAP monitors

[1]Department of Infectious Diseases, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
[2]Department of Pathophysiology, Anhui Medical University, Hefei, Anhui, China
[3]These authors contribute equally
[4]Lead contact
*Correspondence: fanghaoshu@ahmu.edu.cn (H.F.), zzh1974cn@163.com (Z.Z.)
https://doi.org/10.1016/j.isci.2024.110787

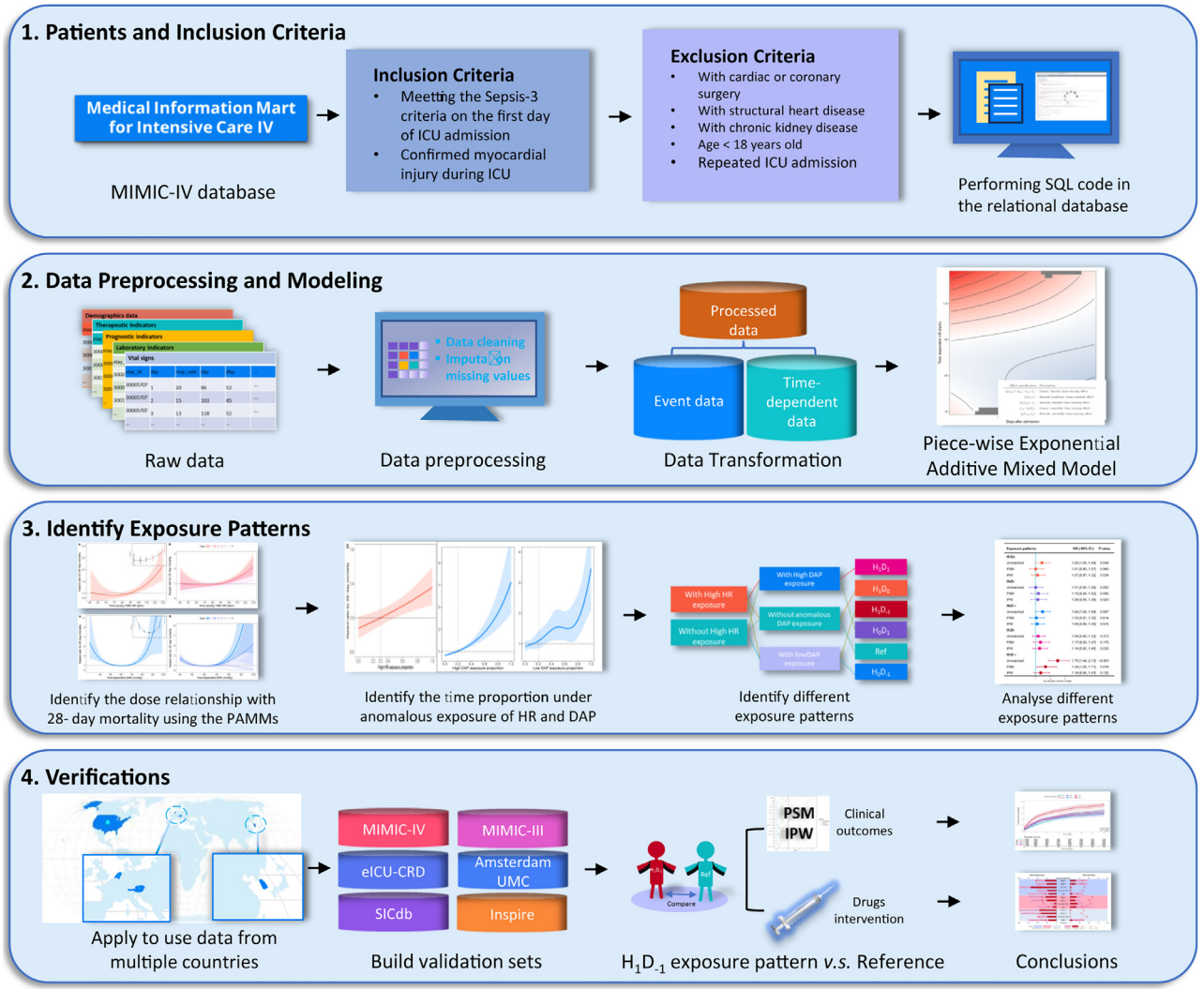


Figure 1. Diagram of the research process

to intricately refine the therapeutic approach for SMI patients, gleaned from insights derived from multicenter real-world data in critically ill settings.

RESULTS

Characteristics of the cohort

We included 20,043 participants: 3,721 (18.6%) from Medical Information Mart for Intensive Care (MIMIC)-IV, 1,153 (5.8%) from MIMIC-III, 8,691 (43.4%) from eICU Collaborative Research Database (eICU-CRD), 1,918 (9.5%) from University of Amsterdam Medical Center database (Amsterdam UMCdb), 4,249 (21.2%) from Salzburg Intensive Care database (SICdb), and 311 (1.5%) from the informative surgical patient dataset for innovative research environment (INSPIRE). Comparing the missing proportions of time-dependent and static indicators in the aforementioned databases, the MIMIC-IV information was the most complete (Figures 1 and S1), so we chose these data as the modeling dataset and internal validation cohort and the remaining five databases as the external validation cohort.

Within the MIMIC-IV database, a total of 3,721 patients with SMI were included in this study. The median age of the patients was 73 years (IQR: 61–83), and 56.5% were male. In the study cohort, 35% of patients had pulmonary infection, 20.9% had urinary infection, and 6.7% had intestinal infection. Additionally, 48.5% of the patients received vasoactive drugs, and 44.2% underwent invasive mechanical ventilation. The median duration of ICU stay was 3.4 days (IQR: 1.8–7.1), with an ICU mortality rate of 23.9% and an overall mortality rate at 7 days of 20% (refer to Table 1).

The validation cohorts, comprising participants from US and European ICUs, along with a collaborative research dataset from Korea named INSPIRE, demonstrated comparability without any discernible age or gender imbalances (Tables S2–S6).

Table 1. Baseline data of the MIMIC-IV database during the first day of ICU admission

Variables	Overall	Survival within 28 days	Death within 28 days	*p* value
N	3,721	2,457	1,264	
Age (years old)	73 (61, 83)	70.9 (59.6, 81.8)	76.0 (63.2, 85.3)	<0.001
Male (%)	2,104 (56.5)	1,410 (57.4)	694 (54.9)	0.158
BMI (kg/m^2)	27.1 (23.3, 32.1)	27.3 (23.4, 32.3)	26.7 (22.8, 31.8)	0.004
Chronic pulmonary disease (%)	1,084 (29.1)	719 (29.3)	365 (28.9)	0.835
Diabetes (%)	1,358 (36.5)	963 (39.2)	395 (31.2)	<0.001
Renal disease (%)	1,209 (32.5)	845 (34.4)	364 (28.8)	0.001
Cerebrovascular disease (%)	645 (17.3)	385 (15.7)	260 (20.6)	<0.001
Hypertension (%)	1,606 (43.2)	1,055 (42.9)	551 (43.6)	0.729
Charlson Comorbidity Score	6 (4, 8)	6 (4, 8)	6 (5, 9)	<0.001
SOFA	7.0 (4, 10)	6 (4, 9)	9.0 (6, 12)	<0.001
SAPS II	45 (36, 55)	41 (34, 50)	53 (42, 64)	<0.001
Pulmonary infection (%)	1,302 (35.0)	852 (34.7)	450 (35.6)	0.600
Intestinal infection (%)	249 (6.7)	171 (7.0)	78 (6.2)	0.399
Urinary infection (%)	779 (20.9)	555 (22.6)	224 (17.7)	0.001
pH	7.3 (7.2, 7.4)	7.3 (7.2, 7.4)	7.3 (7.2, 7.4)	<0.001
PaO_2 (mmHg)	56 (38, 86)	60 (39, 89)	49 (36, 79)	<001
$PaCO_2$ (mmHg)	46 (39, 55)	45 (39, 54)	46 (39, 58)	0.001
Lactate (mmol/L)	2.3 (1.5, 4.3)	2.0 (1.4, 3.5)	3.2 (1.8, 6.3)	<0.001
WBC ($\times 10^9$/L)	14.4 (10.0, 20.6)	13.7 (9.6, 19.6)	15.8 (10.9, 22.3)	<0.001
Hemoglobin (g/dL)	9.7 (8.3, 11.3)	9.8 (8.4, 11.3)	9.5 (8.0, 11.3)	0.031
Platelet ($\times 10^9$/L)	165 (107, 233)	172 (114, 234)	154 (90, 228)	<0.001
Serum creatinine (mg/dL)	1.7 (1.1, 2.9)	1.6 (1.1, 2.9)	1.8 (1.1, 2.9)	0.053
INR	1.4 (1.2, 1.8)	1.3 (1.2, 1.7)	1.5 (1.2, 2.3)	<0.001
Heart rate (bpm)	88 (76, 100)	87 (75, 98)	89 (77, 103)	<0.001
Respiratory rate (/min)	20 (18, 24)	20 (17, 23)	22 (18, 25)	<0.001
SAP (mmHg)	113 (105, 125)	115 (106, 127)	110 (102, 120)	<0.001
DAP (mmHg)	60 (53, 67)	60 (54, 67)	59 (52, 66)	<0.001
Body temperature (°C)	36.8 (36.5, 37.2)	36.8 (36.6, 37.2)	36.8 (36.5, 37.1)	0.001
SpO_2 (%)	97 (95, 98)	97 (96, 98)	97 (95, 99)	<0.001
Urine output (mL/kg/h)	0.6 (0.3, 1.0)	0.7 (0.3, 1.1)	0.4 (0.1, 0.8)	<0.001
RRT (%)	259 (7.0)	166 (6.8)	93 (7.4)	0.539
Vasopressor (%)	1,803 (48.5)	1,018 (41.4)	785 (62.1)	<0.001
Mechanical ventilation (%)	1,646 (44.2)	976 (39.7)	670 (53.0)	<0.001
LOS (days)	3.4 (1.8, 7.1)	3.3 (1.9, 7.4)	3.5 (1.7, 6.9)	0.052
7-day mortality (%)	745 (20.0)	0 (0.0)	745 (58.9)	<0.001
ICU mortality (%)	891 (23.9)	15 (0.6)	876 (69.3)	<0.001

BMI, body mass index; SOFA, Sequential Organ Failure Score; SAPS II, Simplified Acute Physiology Score II; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; WBC, white blood cell count; INR, international standardized ratio; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; SpO_2, percutaneous arterial oxygen saturation; RRT, renal replacement therapy; LOS, length of ICU stay; ICU, intensive care unit.

Modeling and determining exposure patterns

Using the piece-wise exponential additive mixed model (PAMM), we identified the relationship between HR and 28-day mortality rate, which has been consistently increasing, but found a U-shaped relationship between time-dependent DAP and 28-day mortality (Figures 2A and 3A), which was most significant on admission day 1, compared with days 3, 7, and 21 (Figures 2B and 3B).

The findings indicated an elevated mortality risk in patients with SMI when their HR $\geq$ 90 bpm or DAP $\leq$ 50 or >70 mmHg. Conversely, HR < 90 bpm or DAP of 50–70 mmHg further reduced the risk of mortality. Although the strength of the correlation between HR/DAP intensity

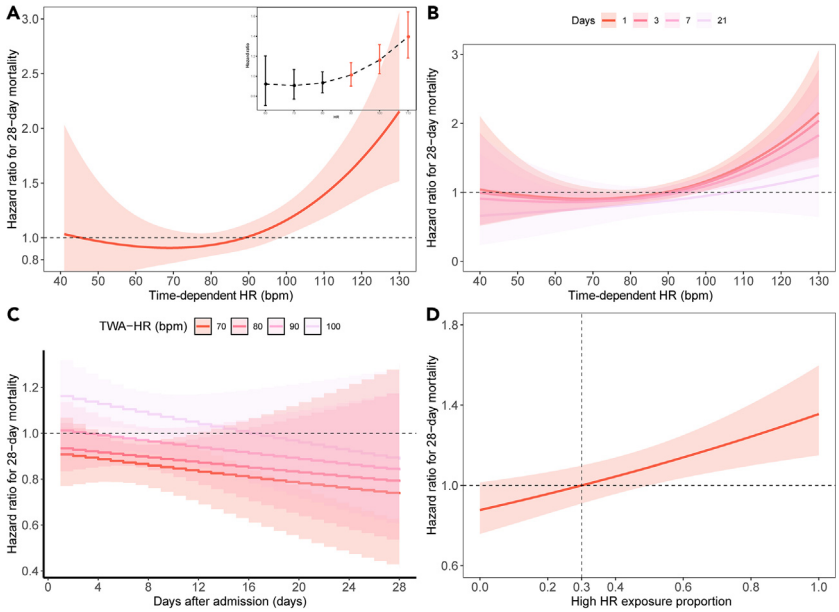


Figure 2. Relationship between daily HR and high HR exposure proportion and 28-day mortality over time using piece-wise exponential additive mixed models

(A) Adjusted relationship between HR over time and 28-day mortality.

(B) Adjusted relationship between HR over time and 28-day mortality stratified by exposure window.

(C) Effect of HR on 28-day mortality over time stratified by level of HR.

(D) Time-dependent effect of high HR exposure proportion on 28-day mortality. Bpm, beat per minute; HR, heart rate.

as measured by HR or DAP and 28-day mortality showed a decreasing trend over time, HR/DAP anomalous exposure in the early stages of ICU admission, especially on day 1, significantly influenced 28-day mortality (Figures 2C and 3C). The hazard ratio for 28-day mortality exhibited a notable elevation when the time-dependent impact of the abnormal exposure proportion was 0.3 for HR and 0.2 for DAP, as illustrated in Figures 2D and 3D. The exhaustive representation of all adjustment variables influencing the impact of time-dependent HR and DAP on 28-day mortality, pertinent to the construction of PAMM models, is delineated in Tables S7–S10.

The association between the distribution of HR and DAP and prognosis among patients with SMI can be succinctly summarized as follows: high HR exposure, especially early, increases 28-day mortality (Figure S2A). Early ICU admission with low or high DAP predicts higher 28-day mortality risk (Figure S2B). Based on the aforementioned observations, the exposures were grouped and patterns modeled. H_0 represents no significant heart rate (HR) exposure, while H_1 indicates high HR exposure, defined as an HR of 90 bpm or higher, with over 30% exposure occurring on day 1. Diastolic arterial pressure (DAP) is divided into three categories: D_0, no high or low exposure; D_1, high exposure (DAP > 70 mmHg, >20% exposure on day 1); and D_{-1}, low exposure (DAP $\leq$ 50 mmHg, >20% exposure on day 1).. The two phenotypes characterized by heightened exposure to HR and the three phenotypes characterized by exposure to DAP were systematically paired, resulting in the delineation of six distinct patterns: H_1D_1, H_1D_0, H_1D_{-1}, H_0D_1, H_0D_{-1}, alongside the baseline pattern devoid of abnormal exposure designated as H_0D_0, serving as the reference (Ref).

Within the interactivity analysis, the preeminent determinant of hazard ratio in the H_1D_1 pattern was the elevated DAP exposure proportion (Figure S3A). Conversely, in the H_1D_{-1} pattern, an interactive effect was discerned between elevated HR and diminished DAP exposure (Figure S3B). Mediation analyses conducted through lactate levels revealed that both elevated HR (Figure S4A), elevated DAP (Figure S4B), and diminished DAP (Figure S4C) independently contributed to mortality via direct effects. This implies a synergistic influence of heightened HR exposure and reduced DAP exposure, potentially leading to increased mortalities through the direct dysfunction of macrovascular circulation.

Analysis of exposure patterns

Comparing each exposure pattern to the reference for baseline characteristics, key distinctions emerge: H_1D_0 exhibits increased vasopressor use, faster respiratory rates, and higher pulmonary infection rates (Figure S5A). H_0D_1 is associated with higher occurrences of cerebrovascular and hypertension diseases at a younger age (Figure S5B). H_0D_{-1} is characterized by an older demographic, more females, and a higher prevalence of renal disease and diabetes (Figure S5C). H_1D_1 displays faster respiratory rates, higher body temperature, and increased intestinal infection rates (Figure S5D). H_1D_{-1}, with the most severe baseline characteristics, shows higher Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPS II) scores, increased vasopressor use, faster respiratory rates, higher body temperature, and more intestinal infections and chronic pulmonary disease (Figure S5E).

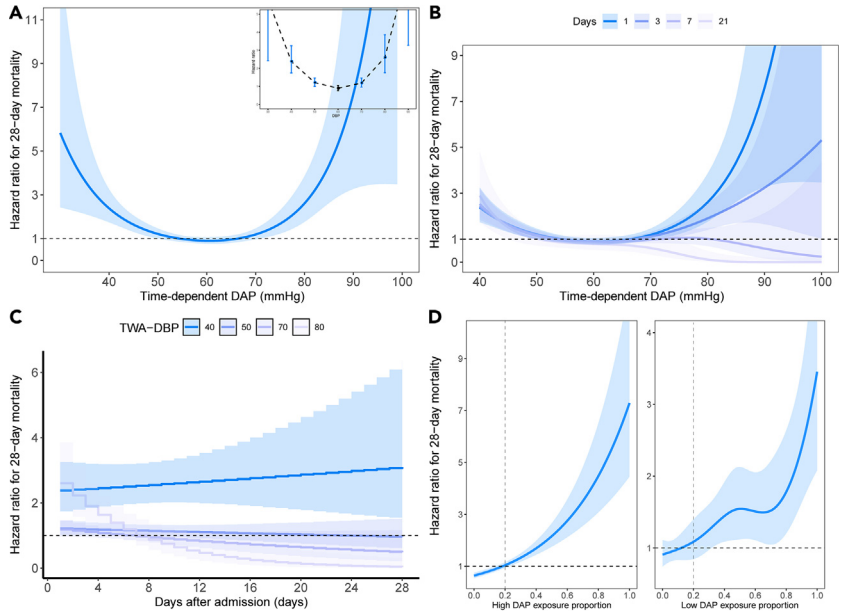


Figure 3. Relationship between daily DAP and hazardous DAP exposure proportion and 28-day mortality over time using piece-wise exponential additive mixed models

(A) Adjusted relationship between DAP over time and 28-day mortality.

(B) Adjusted relationship between DAP over time and 28-day mortality stratified by exposure window.

(C) Effect of DAP on 28-day mortality over time stratified by level of DAP.

(D) Time-dependent effect of high and low DAP exposure proportion on 28-day mortality. DAP, diastolic arterial pressure.

There are also differences in organ function injuries for each pattern. Organ injury is assessed using the six sub-items of the SOFA score. Patients with sepsis often have a combination of multiple organ dysfunction, primarily circulatory, respiratory, and renal (Figure S6A), while H_1D_{-1} has the most critical organ impairment of all exposure patterns (Figure S6B). High HR exposure alone was often associated with cardiovascular and respiratory injury, and low DAP exposure alone is also often combined with cardiac injury (Figure S6A). Considering baseline characteristics, organ damage, and the synergistic impact of high HR and low DAP on mortality among patients exhibiting the H_1D_{-1} exposure pattern, we advocate for focusing our attention on this specific exposure characterization within the population.

Of the six exposure patterns, H_1D_{-1} consistently demonstrated significantly higher mortalities across all time points ($p < 0.001$, Figure 4). Subgroup analysis for H_1D_{-1} exposed patients indicated a 7-day mortality hazard ratio of 2.19 (95% confidence interval [CI] 1.69–2.86), surpassing the 28-day mortality hazard ratio of 1.75 (95% CI 1.44–2.13). Elevated 28-day mortality risks were observed among individuals under 65 years old, females, and those with respiratory or intestinal infections in conjunction with chronic lung disease, diabetes mellitus, renal disease, and hypertension (Figure S7). For external validation, H_1D_{-1} consistently exhibited the highest 28-day mortality rate across five datasets, supporting its significance ($p < 0.001$, Figures S8 and S9).

Characteristics and validation of clinical outcomes

In the MIMIC-IV database, notable disparities in mortality rates across various exposure patterns (Figure 4) and divergences in baseline information (Figure S5) were observed, signifying that not all exposure patterns yielded unfavorable outcomes. Specifically, the H_1D_{-1} pattern emerged as a consistent and robust indicator of heightened risk for predicting 28-day mortality. Rigorous validation across five datasets from diverse global locations consistently underscored significantly elevated mortality rates associated with H_1D_{-1} in comparison to alternative exposure patterns. Post-application of methodological refinements such as propensity score matching and inverse probability weighting to align baseline data, the findings portrayed sustained stability. This underscores the extensive applicability of this particular representation across a broad spectrum of geographic regions and demographic compositions (Figures 4 and S8–S13). Additionally, the receiver operating characteristic curves revealed that our H_1D_{-1} exposure pattern more accurately predicts 28-day mortality in patients with sepsis, with consistent results across various regional populations (Figure S14). However, the distribution of troponin levels was not stable across phenotypic patient groups (Figures S15–S20). This finding indicates that early myocardial injury marked by elevated troponin does not necessarily correlate with increased mortality.

The relationship between drug administration and clinical outcomes

Given that the characterization of H_1D_{-1} primarily involves HR and diastolic blood pressure, we deliberately chose three medications with potential impacts on these parameters to assess the therapeutic response of this characterization to cardiac drugs. The selected drugs include

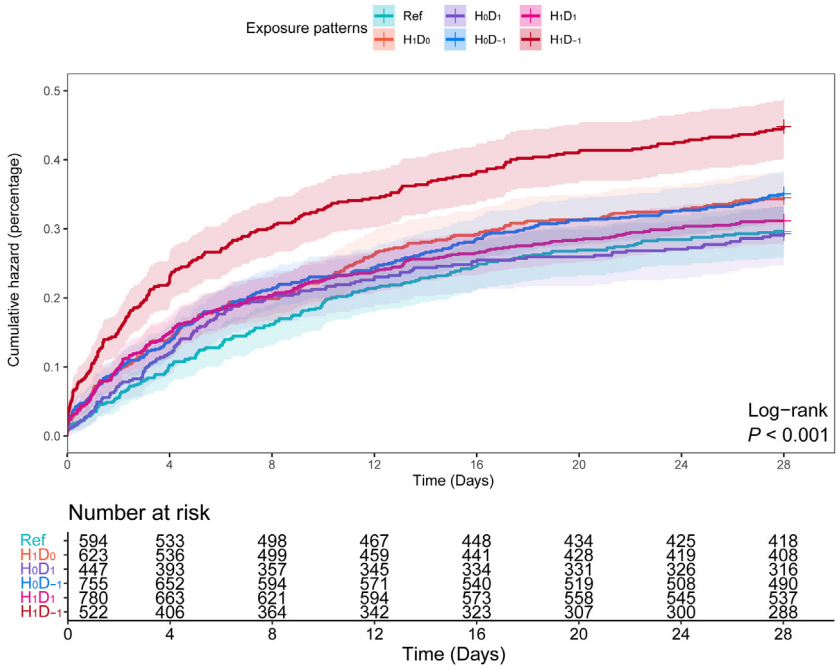


Figure 4. Kaplan-Meier curves for the six exposure patterns in the MIMIC-IV set

negative inotropic drugs, glucocorticoids, and ascorbic acid. As illustrated in Figure S21, no significant difference in mortality was observed with or without negative inotropes and necrotic acid within the Ref group. Nevertheless, analyses from the MIMIC IV, Amsterdam UMCdb, and SICdb databases indicated a noteworthy increase in mortality risk associated with the use of glucocorticoids ($p < 0.05$). Varied outcomes have been noted regarding the effectiveness of negative inotropes in reducing mortality among patients with the H_1D_{-1} pattern. Notably, no significant difference was identified in the impact of ascorbic acid on mortality risk, regardless of supplementation. In contrast, the use of glucocorticoids markedly escalated the risk of mortality, and this observation remained consistent across the remaining four databases ($p < 0.05$) (Figure S22). Moreover, we estimated the hazard ratios for 28-day mortality in patients with SMI who exhibited the H_1D_{-1} exposure pattern with various pharmacologic interventions. The results showed instability both with and without administration of negative inotropic drugs and ascorbic acid. Of great interest, the results from the other four databases consistently underscored the association between glucocorticoid use and a significantly increased risk of mortality (Figure 5).

DISCUSSION

In our exploratory and retrospective quantitative analysis, we observed a potential association between early irregularities in HR and DAP and heightened 28-day mortality among patients with SMI. Further investigation highlighted the H_1D_{-1} pattern as a high-risk exposure profile within the SMI cohort. A subsequent secondary analysis outlined the clinical characteristics of patients exhibiting the H_1D_{-1} exposure pattern, indicating initial indications that glucocorticoids use in these individuals might not support patient recovery. Moreover, to reinforce the reliability of this conclusion, we conducted additional validation using data sourced from diverse regions.

Considerable evidence suggested that high HR can be considered a strong predictor of cardiovascular morbidity and mortality in various clinical settings.[10] In the early stages of sepsis, activation of the sympathetic nervous system resulted in a compensatory increase in HR and peripheral vasoconstriction to preserve cardiac output; however, the compensatory neuroendocrine response became overwhelming as the disease progressed. Prolonged sympathetic hyperactivity may also reverse adrenergic G-protein coupling from a stimulatory to an inhibitory response, causing severe myocardial depression and reduced sensitivity to vasopressin observed in certain septic patients.[11] Increased nitric oxide (NO) production mediates peripheral vascular dysfunction and reduced arterial compliance, which, in combination with the vasoparalytic state typical of septic shock, also lead to an increased HR.[12] A Morelli et al. found that using the beta blocker esmolol may improve systemic perfusion in septic shock by reducing HR and arterial elastance.[13] Hypotension in sepsis arises from a complex interaction between vasodilation, modified blood-flow distribution, relative and absolute hypovolemia, and myocardial dysfunction. The accumulation of NO led to sustained smooth muscle diastole, and vasodilation played a key role in the development of hypotension and inadequate tissue perfusion in septic shock.[11] A study showed DAP to be superior to SAP in predicting prognosis of cardiogenic shock, with performance similar to SOFA score[14]; DAP on the first day of admission was independently associated with 24-day mortality.[14] Although the definition of septic shock did not include DAP,[15] research had demonstrated that low DAP usually reflects severe vasodilatation and was associated with increased mortality.[16] Further research had confirmed that the bias of DAP measurements was significantly lower than that of SAP and was less susceptible to

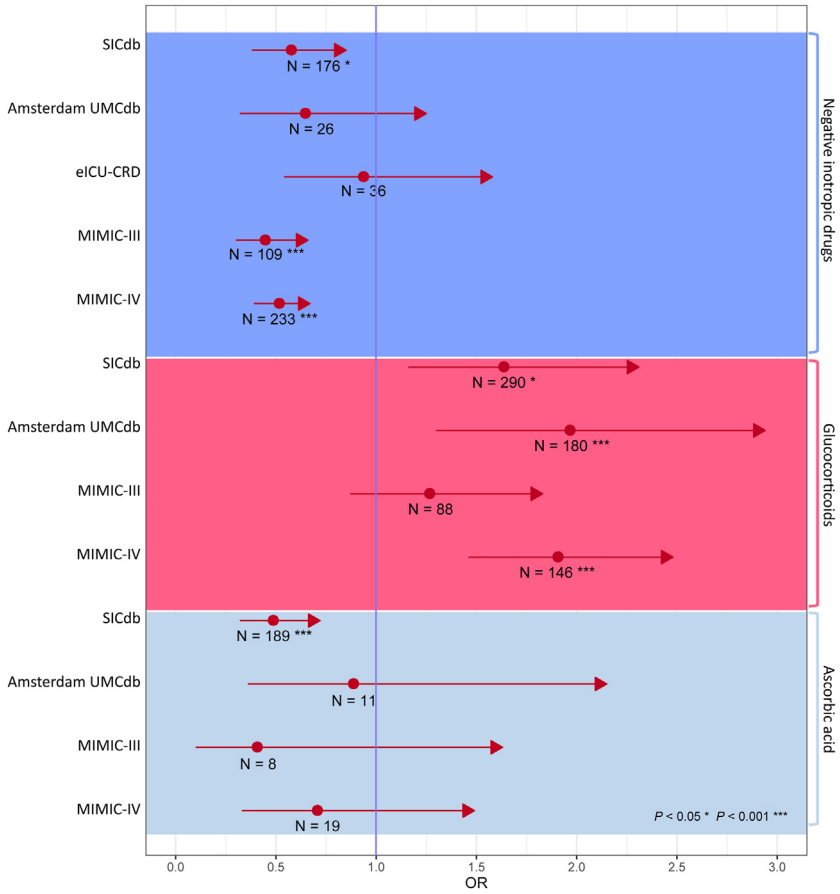


Figure 5. The hazard ratio for 28-day mortality in patients with the H_1D_{-1} phenotype estimated using the Cox proportional risk model under the influence of negative inotropes, glucocorticoids, and ascorbic acid

pulse wave reflection, measurement method, and other related factors.[17] A large community-based cohort demonstrated that DAP was also a primary determinant of coronary perfusion pressure,[18] critical for maintaining adequate post-resuscitation myocardial perfusion. The combination of DAP and HR can reflect the degree of circulatory dysfunction during vasodilation due to the robust relationship between blood pressure and blood flow.[14] As vascular tone progressively decreased, gradually higher HR did not compensate for the decrease in DAP, and the relative risk of death increased proportionally. In septic shock patients with tachycardia, elevated diastolic shock index (DSI) (DAP/HR) values were linked to an increased mortality risk.[14] Research was ongoing to identify adjuvant therapies that were safe and effective to preserve organ function and reduce mortality in sepsis patients. The heart is a key organ that is susceptible to sepsis. However, despite significant advances in treating sepsis, these approaches have failed to fully address myocardial injury. There were no specific treatment recommendations for SMI. The pathogenesis of sepsis involves a variety of complex processes. Oxidative stress is a major mechanism of SMI. Vitamin C (VC), also known as ascorbic acid, is a potent antioxidant, reducing oxidative stress and inflammation, improving vasopressor synthesis, enhancing immune cell function and endovascular function, reducing myocardial apoptotic damage and inflammatory storms, increasing autophagy, and ultimately protecting the myocardium. VC benefits the heart in sepsis patients, reducing myocardial damage and inflammation,[19] but some studies have shown the opposite.[20] Marik concluded that VC levels are significantly lower in most sepsis patients[21] and VC supplementation can help to reduce myocardial damage in sepsis patients. Furthermore, animal experiments have demonstrated that VC-deficient mice are more susceptible to sepsis-induced multi-organ dysfunction, and a high-dose of vitamin C demonstrated a protective effect against SMI in rats, as evidenced by a significant reduction in serum markers of myocardial damage.[22] We did not observe a reduction in mortality with VC supplementation, which may be related to the fact that the dose and duration of VC administration were not included in the study, and prospective studies on the dose-response relationship are imperative. In SMI, the myocardium is in a state of hibernation, accompanied by a reduction in cardiac output. Consequently, patients with myocardial depression require the administration of positive inotropic drugs to achieve adequate tissue perfusion and improve hemodynamics. However, prolonged administration, particularly at doses that are not clinically necessary, may exacerbate myocardial injury. Nevertheless, the use of negative inotropic drugs in patients with SMI is a matter of contention. Beta blockers are beneficial in the treatment of numerous cardiovascular diseases. Landiolol[23] and esmolol[24] have been shown to reduce the risk of myocardial ischemia in septic patients without the systemic consequences of inadequate perfusion.

Schmittinger demonstrated that the combination of milrinone with the beta blocker metoprolol resulted in a low HR, higher output per beat, and thus better preserved cardiac function.[25] Beta blockers may benefit SMI, but there are few relevant studies. Our study could not confirm that negative inotropic drugs improve the prognosis of SMI, and further studies may be needed to investigate the effect of the net balance between positive and negative inotropic drugs on clinical outcomes. The inflammatory cytokines tumor necrosis factor alpha and interleukin-6 play a pivotal role in the pathogenesis of septic myocardial injury. Glucocorticoids are regarded as potent regulators of the inflammatory response, with the capacity to inhibit cardiomyocyte apoptosis, enhance cardiac contractile performance, and modulate cardiac injury following reperfusion. Consequently, exogenous steroid hormones have been demonstrated to exert cytoprotective effects on cardiomyocytes. Nevertheless, during ischemic stress, blood levels of catecholamines are significantly elevated, and the proarrhythmic and catabolic effects of glucocorticoids on the heart may exhibit adverse effects on the circulatory system. It should be noted that glucocorticoids have the potential to exert a negative effect on the severity of schizophrenia, with elevated levels of glucocorticoids in H1D-1 pattern being associated with adverse outcomes.

Prognosis and fluid resuscitation were usually assessed clinically based on macroscopic hemodynamic characteristics. In early shock, the circulation compensates by activating the sympathetic nervous system and redistributes blood. Reflecting this compensatory mechanism, the shock index (HR/SAP),[26] modified shock index (HR/mean arterial pressure [MAP]), and diastolic shock index (HR/DAP)[14] had been used to predict the prognosis of various diseases. However, this was based on data collected at a single point in time, and the complex hemodynamic characteristics of most critically ill septic patients evaluated with the aforementioned measurements were likely to influence the assessment. It was known that delayed correction of hypotension was associated with a poor prognosis. The Surviving Sepsis Campaign guidelines recommend maintaining MAP $\geq$ 65 mmHg.[1] However, our study addresses a clinical need as there was a lack of research providing precise blood pressure thresholds for patients with SMI experiencing acute cardiac and vascular dysfunction and analyses of HR and DAP as time-dependent variables in PAMM to explore their impact over time. Our study provided precise definitions, including cutoff values for abnormal HR and DAP, as well as the proportion of exposure time. As a tool for early identification of high-risk patients and prognostic assessment, we confirmed the H_1D_{-1} exposure pattern, which was simple and easy to implement. No further invasive measurements were required, and this technique allowed assessment of dynamic hemodynamics. Upon exposure to H_1D_{-1}, it can serve as a clinical practice standard for the incorporation of vasopressors in non-fluid reactive patients, enabling prompt restoration of tissue perfusion and preventing injury caused by fluid overload.[16] We employed the authoritative MIMIC-IV database for modeling, which has undergone validation in five other databases covering multi-center efforts in Asia, Europe, and the Americas, and we confirmed this exposure pattern was stable and reliable. Rapid recognition of high-risk patterns combined resuscitation strategies can directly benefit most healthcare organizations. In addition, to validate its clinical effectiveness, we conducted a secondary analysis to estimate the benefits and costs of exposure model-guided medical interventions in SMI patients. The results showed that patients in the H_1D_{-1} exposure pattern had a significantly increased risk of death with glucocorticoids. Although we cannot answer the question of whether ascorbic acid and negative inotropes can be a benefit to septic patients, we support glucocorticoids did not benefit SMI patients, especially H_1D_{-1}.

Conclusions

In conclusion, our study has identified a distinctive clinical feature grounded in early HR and diastolic blood pressure among patients with SMI, with DAP $\leq$ 50 mmHg (duration proportion > 0.3) and HR $\geq$ 90 bpm (duration proportion > 0.2). In populations exhibiting this exposure pattern, preliminary evidence suggests that the use of glucocorticoids is detrimental to prognosis, and further prospective research is warranted to deepen our understanding and validate these findings.

Limitations of the study

Our study was designed as a retrospective observational study. Although we included a considerable number of variables to correct for bias, there may still be confounders and potential biases that were not controlled for. Particularly for drug validation, the total number of cases was poor. It was not possible to analyze subgroup comparisons of treatment window, drug dose, duration, and drug type. The number of cases in some databases did not meet the sample size requirements for model derivation, so validation was not performed in all databases. Secondly, although we had data from Europe, America, and Asia, the amount of data in the Korean database was small. Last but not the least, future prospective validation was necessary to confirm the robustness of the exposure pattern and its potential to predict other septic organ damage.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact Zhenhua Zhang (zzh1974cn@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The data required to replicate these findings are available from the lead contact upon reasonable request.

- Code: the code used for the analyses is available from the lead author.
- To further facilitate communication among interested readers, we have created corresponding modules on GitHub and uploaded our code and data to promote scientific openness and collaboration. You can access these resources at https://github.com/jaser1314/Sepsismyocardialinjury/tree/main.
- The datasets generated or analyzed during this study are available in their entirety upon request.

ACKNOWLEDGMENTS

The authors are grateful for all the researchers for making data publicly available and thank the developers of R software and R packages for their contributions and convenience.

The study was supported by Anhui Provincial Natural Science Foundation, no. 2108085MH298.

AUTHOR CONTRIBUTIONS

Conceptualization, W.L., H.F., and Z.Z.; methodology, W.L., J.D., and P.Z.; investigation, P.Z., Y.Z., and M.N.; writing – original draft, W.L., J.D., and P.Z.; writing – review and editing, H.F. and Z.Z.; funding acquisition, Z.Z.; resources, H.F. and Z.Z.; supervision, W.L., H.F., and Z.Z.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
- METHOD DETAILS
  - Data sources
  - Study population
  - Variables and outcomes
- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110787.

Received: April 27, 2024
Revised: June 6, 2024
Accepted: August 19, 2024
Published: August 22, 2024

REFERENCES

1. Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C.M., French, C., Machado, F.R., McIntyre, L., Ostermann, M., Prescott, H.C., et al. (2021). Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. *47*, 1181–1247. https://doi.org/10.1007/s00134-021-06506-y.
2. Hollenberg, S.M., and Singer, M. (2021). Pathophysiology of sepsis-induced cardiomyopathy. Nat. Rev. Cardiol. *18*, 424–434. https://doi.org/10.1038/s41569-020-00492-2.
3. Ehrman, R.R., Sullivan, A.N., Favot, M.J., Sherwin, R.L., Reynolds, C.A., Abidov, A., and Levy, P.D. (2018). Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. Crit. Care *22*, 112. https://doi.org/10.1186/s13054-018-2043-8.
4. Thygesen, K., Alpert, J.S., Jaffe, A.S., Chaitman, B.R., Bax, J.J., Morrow, D.A., and White, H.D.; Executive Group on behalf of the Joint European Society of Cardiology ESC/American College of Cardiology ACC/American Heart Association AHA/World Heart Federation WHF Task Force for the Universal Definition of Myocardial Infarction (2018). Fourth Universal Definition of Myocardial Infarction (2018). Circulation *138*, e618–e651. https://doi.org/10.1161/cir.0000000000000617.
5. Merx, M.W., and Weber, C. (2007). Sepsis and the heart. Circulation *116*, 793–802. https://doi.org/10.1161/circulationaha.106.678359.
6. Lamia, B., Teboul, J.L., Monnet, X., Osman, D., Maizel, J., Richard, C., and Chemla, D. (2007). Contribution of arterial stiffness and stroke volume to peripheral pulse pressure in ICU patients: an arterial tonometry study. Intensive Care Med. *33*, 1931–1937. https://doi.org/10.1007/s00134-007-0738-4.
7. Vidal-Petiot, E., Ford, I., Greenlaw, N., Ferrari, R., Fox, K.M., Tardif, J.C., Tendera, M., Tavazzi, L., Bhatt, D.L., and Steg, P.G.; CLARIFY Investigators (2016). Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet *388*, 2142–2152. https://doi.org/10.1016/s0140-6736(16)31326-5.
8. Vincent, J.L., and De Backer, D. (2013). Circulatory shock. N. Engl. J. Med. *369*, 1726–1734. https://doi.org/10.1056/NEJMra1208943.
9. Siegel, J.H., Greenspan, M., and Del Guercio, L.R. (1967). Abnormal vascular tone, defective oxygen transport and myocardial failure in human septic shock. Ann. Surg. *165*, 504–517. https://doi.org/10.1097/00000658-196704000-00002.
10. Danzi, G.B., and Cuspidi, C. (2017). Diastolic Blood Pressure and Myocardial Damage: What About Coronary Perfusion Time? J. Am. Coll. Cardiol. *69*, 1645–1646. https://doi.org/10.1016/j.jacc.2016.11.086.
11. Lv, X., and Wang, H. (2016). Pathophysiology of sepsis-induced myocardial dysfunction. Mil. Med. Res. *3*, 30. https://doi.org/10.1186/s40779-016-0099-9.
12. Hayano, J., and Yasuma, F. (2003). Hypothesis: respiratory sinus arrhythmia is an intrinsic resting function of cardiopulmonary system. Cardiovasc. Res. *58*, 1–9. https://doi.org/10.1016/s0008-6363(02)00851-9.
13. Morelli, A., Singer, M., Ranieri, V.M., D'Egidio, A., Mascia, L., Orecchioni, A., Piscioneri, F., Guarracino, F., Greco, E., Peruzzi, M., et al. (2016). Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. Intensive Care Med. *42*, 1528–1534. https://doi.org/10.1007/s00134-016-4351-2.

14. Ospina-Tascón, G.A., Teboul, J.L., Hernandez, G., Alvarez, I., Sánchez-Ortiz, A.I., Calderón-Tapia, L.E., Manzano-Nunez, R., Quiñones, E., Madriñan-Navia, H.J., Ruiz, J.E., et al. (2020). Diastolic shock index and clinical outcomes in patients with septic shock. Ann. Intensive Care *10*, 41. https://doi.org/10.1186/s13613-020-00658-8.
15. Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G.R., Chiche, J.D., Coopersmith, C.M., et al. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA *315*, 801–810. https://doi.org/10.1001/jama.2016.0287.
16. Ospina-Tascón, G.A., Hernandez, G., Alvarez, I., Calderón-Tapia, L.E., Manzano-Nunez, R., Sánchez-Ortiz, A.I., Quiñones, E., Ruiz-Yucuma, J.E., Aldana, J.L., Teboul, J.L., et al. (2020). Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. Crit. Care *24*, 52. https://doi.org/10.1186/s13054-020-2756-3.
17. Lehman, L.w.H., Saeed, M., Talmor, D., Mark, R., and Malhotra, A. (2013). Methods of blood pressure measurement in the ICU. Crit. Care Med. *41*, 34–40. https://doi.org/10.1097/CCM.0b013e318265ea46.
18. McEvoy, J.W., Chen, Y., Rawlings, A., Hoogeveen, R.C., Ballantyne, C.M., Blumenthal, R.S., Coresh, J., and Selvin, E. (2016). Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events: Implications for Blood Pressure Control. J. Am. Coll. Cardiol. *68*, 1713–1722. https://doi.org/10.1016/j.jacc.2016.07.754.
19. Lankadeva, Y.R., Peiris, R.M., Okazaki, N., Birchall, I.E., Trask-Marino, A., Dornom, A., Vale, T.A.M., Evans, R.G., Yanase, F., Bellomo, R., and May, C.N. (2021). Reversal of the Pathophysiological Responses to Gram-Negative Sepsis by Megadose Vitamin C. Crit. Care Med. *49*, e179–e190. https://doi.org/10.1097/ccm.0000000000004770.
20. Mitchell, A.B., Ryan, T.E., Gillion, A.R., Wells, L.D., and Muthiah, M.P. (2020). Vitamin C and Thiamine for Sepsis and Septic Shock. Am. J. Med. *133*, 635–638. https://doi.org/10.1016/j.amjmed.2019.07.054.
21. Marik, P.E. (2018). Hydrocortisone, Ascorbic Acid and Thiamine (HAT Therapy) for the Treatment of Sepsis. Focus on Ascorbic Acid. Nutrients *10*, 1762. https://doi.org/10.3390/nu10111762.
22. Cui, Y.N., Tian, N., Luo, Y.H., Zhao, J.J., Bi, C.F., Gou, Y., Liu, J., Feng, K., and Zhang, J.F. (2024). High-dose Vitamin C injection ameliorates against sepsis-induced myocardial injury by anti-apoptosis, anti-inflammatory and pro-autophagy through regulating MAPK, NF-κB and PI3K/AKT/mTOR signaling pathways in rats. Aging (Albany NY) *16*, 6937–6953. https://doi.org/10.18632/aging.205735.
23. Hagiwara, S., Iwasaka, H., Maeda, H., and Noguchi, T. (2009). Landiolol, an ultrashort-acting beta1-adrenoceptor antagonist, has protective effects in an LPS-induced systemic inflammation model. Shock *31*, 515–520. https://doi.org/10.1097/SHK.0b013e3181863689.
24. Gore, D.C., and Wolfe, R.R. (2006). Hemodynamic and metabolic effects of selective beta1 adrenergic blockade during sepsis. Surgery *139*, 686–694. https://doi.org/10.1016/j.surg.2005.10.010.
25. Schmittinger, C.A., Dünser, M.W., Haller, M., Ulmer, H., Luckner, G., Torgersen, C., Jochberger, S., and Hasibeder, W.R. (2008). Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. Crit. Care *12*, R99. https://doi.org/10.1186/cc6976.
26. Allgöwer, M., and Burri, C. (1967). ["Shock index"]. Dtsch. Med. Wochenschr. *92*, 1947–1950. https://doi.org/10.1055/s-0028-1106070.
27. Johnson, A.E.W., Bulgarelli, L., Shen, L., Gayles, A., Shammout, A., Horng, S., Pollard, T.J., Hao, S., Moody, B., Gow, B., et al. (2023). MIMIC-IV, a freely accessible electronic health record dataset. Sci. Data *10*, 1. https://doi.org/10.1038/s41597-022-01899-x.
28. Johnson, A.E.W., Pollard, T.J., Shen, L., Lehman, L.W.H., Feng, M., Ghassemi, M., Moody, B., Szolovits, P., Celi, L.A., and Mark, R.G. (2016). MIMIC-III, a freely accessible critical care database. Sci. Data *3*, 160035. https://doi.org/10.1038/sdata.2016.35.
29. Pollard, T.J., Johnson, A.E.W., Raffa, J.D., Celi, L.A., Mark, R.G., and Badawi, O. (2018). The eICU Collaborative Research Database, a freely available multi-center database for critical care research. Sci. Data *5*, 180178. https://doi.org/10.1038/sdata.2018.178.
30. Thoral, P.J., Peppink, J.M., Driessen, R.H., Sijbrands, E.J.G., Kompanje, E.J.O., Kaplan, L., Bailey, H., Kesecioglu, J., Cecconi, M., Churpek, M., et al. (2021). Sharing ICU Patient Data Responsibly Under the Society of Critical Care Medicine/European Society of Intensive Care Medicine Joint Data Science Collaboration: The Amsterdam University Medical Centers Database (AmsterdamUMCdb) Example. Crit. Care Med. *49*, e563–e577. https://doi.org/10.1097/ccm.0000000000004916.
31. Rodemund, N., Wernly, B., Jung, C., Cozowicz, C., and Koköfer, A. (2023). The Salzburg Intensive Care database (SICdb): an openly available critical care dataset. Intensive Care Med. *49*, 700–702. https://doi.org/10.1007/s00134-023-07046-3.
32. Goldberger, A.L., Amaral, L.A., Glass, L., Hausdorff, J.M., Ivanov, P.C., Mark, R.G., Mietus, J.E., Moody, G.B., Peng, C.K., and Stanley, H.E. (2000). PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation *101*, E215–E220. https://doi.org/10.1161/01.cir.101.23.e215.
33. Bender, A., Groll, A., and Scheipl, F. (2018). A generalized additive model approach to time-to-event analysis. Stat. Model. Int. J. *18*, 299–321. https://doi.org/10.1177/1471082X17748083.
34. Robins, J. (1986). A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math. Model. *7*, 1393–1512. https://doi.org/10.1016/0270-0255(86)90088-6.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
the Medical Information Mart for Intensive Care IV database (MIMIC-IV, version 2.2)	https://physionet.org/content/mimic4-carevue/1.4/	N/A
the Medical Information Mart for Intensive Care III database (MIMIC-III, version 1.4)	https://phyonet.org/content/mimiciv/2.2/	N/A
the eICU Collaborative Research Database (eICU-CRD)	https://physionet.org/about/database/	N/A
the University of Amsterdam Medical Center database (Amsterdam UMCdb, version 1.0.2)	https://amsterdammedicaldatascience.nl/	N/A
the Salzburg Intensive Care database (SICdb, version 1.0.6)	https://physionet.org/about/database/	N/A
the INSPIRE dataset (version 1.0)	https://physionet.org/about/database/	N/A
Software and algorithms		
R software version 4.2.2	R Foundation for Statistical Computing, Vienna, Austria	N/A

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

In the course of our retrospective and exploratory study concerning patients with sepsis-associated myocardial injury, we undertook a comprehensive approach by leveraging data derived from multiple centers. This strategic choice was made to bolster the generalizability of our study's outcomes. It is noteworthy that these datasets have undergone rigorous ethical review by local hospitals in advance, and meticulous de-identification procedures have been implemented to safeguard patient privacy. As a result, we are granted access to ethical content from the official websites of these data centers, ensuring adherence to the highest ethical standards in our research endeavors.

METHOD DETAILS

Data sources

Our multi-center dataset was diligently curated from six prominent publicly available critical care databases, namely the Medical Information Mart for Intensive Care IV database (MIMIC-IV, version 2.2),[27] the Medical Information Mart for Intensive Care III database (MIMIC-III, version 1.4),[28] the eICU Collaborative Research Database (eICU-CRD),[29] the University of Amsterdam Medical Center database (Amsterdam UMCdb, version 1.0.2),[30] the Salzburg Intensive Care database (SICdb, version 1.0.6),[31] and the INSPIRE dataset (version 1.0).[32]

Study population

The study involved patients who were diagnosed with sepsis and myocardial injury during their ICU admission. Sepsis was defined based on the Third International Consensus Criteria for Sepsis,[15] which include suspicion of infection and a Sequential Organ Failure Assessment (SOFA) score of 2 or higher. The updated sepsis criteria lack definitiveness for suspected infections. In light of this, the administration of antibiotics or the collection of blood culture specimens was deemed indicative of a suspected infection within the study. Myocardial injury was defined in accordance with the European Heart Association's criteria, specifically referencing the 99th percentile of troponin levels above the upper referential boundary. This stringent definition ensured a precise identification of myocardial injury cases within the patient cohort.[4] Following the defined criteria, patients with cardiac surgery, coronary surgery, structural heart disease, chronic kidney disease [identified by International Classification of Diseases (ICD) codes], minors, and repeat admissions were excluded. This exclusion strategy aimed to enhance the consistency and homogeneity of baseline data in the study cohort.

Variables and outcomes

To comprehensively assess the impact on outcomes, we implemented an analytical framework encompassing demographics, laboratory indicators, organ scores, vital signs, and therapeutic indicators. Extraction strategies varied for clinically characterized variables. Demographic data (age, gender, body mass index) were derived from the first recorded values at admission. Binary extraction, utilizing ICD codes, was employed for comorbidity, infection site, and therapeutic indicators. Clinical scores (e.g., Sequential Organ Failure Score-SOFA, Simplified Acute Physiology Score-SAPS) were calculated as maximum values on the first day of ICU admission. Laboratory indicators were derived

from the worst values based on clinical experience. Vital signs were dynamically quantified using a time-weighted average (calculated as the area under the time curve divided by the time) for each day.

Our primary outcome measure was 28-day mortality, represented as binary data. Secondary outcomes, including 7-day mortality and length of ICU stay (LOS), provided supplementary insights. Table S1 offers a comprehensive summary of all variables to be analyzed, each meticulously described for thorough characterization.

QUANTIFICATION AND STATISTICAL ANALYSIS

In the current study, chi-square tests served as the analytical tool for comparing binary variables, and their presentation involved enumerative counts and respective percentages. The evaluation of numerical variables entailed the application of the Mann-Whitney U-test, with descriptors comprising the median and interquartile range. To ascertain the robustness of our datasets, a meticulous assessment was conducted, revealing the MIMIC-IV dataset as the most comprehensive and suitable for modeling, derivation, and characterization analyses. This discernment is visually conveyed in Figure S1.

In addressing missing values on the initial ICU admission day, we used Multiple Interpolation based on Fully Conditional Specification to replace missing values if they were less than 50%, and excluded those that were more than 50% missing. Subsequently, we proceeded with modeling and statistical analyses. To elucidate the dynamic impact of heart rate and diastolic blood pressure on the temporal trajectory of mortality, we employed time-varying relative effects within recursive event-based Piece-wise exponential Additive Mixed Model (PAMM).[33] This approach facilitated the estimation of dose, time window, and time fraction pertaining to hazardous exposure. Covariates underwent rigorous backward screening to ascertain their significance, followed by secondary analyses focused on exposure characterization based on these outcomes. In an effort to ensure a more equitable comparison of clinical outcomes, we derived two distinct cohorts comprising exposed and unexposed patients via propensity score matching (PSM) and inverse probability weighting (IPW).[34] This approach aimed to establish a balanced baseline at admission, a methodology consistently applied for baseline correction in validation sets. Furthermore, we maintained uniformity by employing the same data extraction approach across verified datasets. Given the inherent limitations stemming from data integrity and sample size constraints within specific databases, we selectively validated the research findings.

All statistical analyses were executed utilizing R (version 4.2.2), an open-source statistical programming language. The criterion for statistical significance was established as p values less than 0.05, aligning with conventional thresholds in scientific research.

ADDITIONAL RESOURCES

This study did not create or add to a new website, nor was it part of a clinical trial.