Cardiovascular Diabetology

REVIEW

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Relationship between stress hyperglycaemic ratio (SHR) and critical illness: a systematic review

Guoyuan Song[1], Xiujuan Liu[2], Zihe Lu[2], Jingyue Guan[1], Xinyue Chen[1], Yichen Li[1], Gang Liu[1], Gang Wang[1*] and Fangfang Ma[1*]

Abstract

Stress-induced hyperglycemia (SIH) is a physiological response to acute or chronic stress characterized by elevated blood glucose levels. It is prevalent in both patients with and without diabetes, particularly those with acute or critical illnesses. The development of SIH is characterized by complex interactions among catecholamines, cortisol, and inflammatory mediators such as cytokines, resulting in increased hepatic glucose production and insulin resistance. While mild to moderate SIH may provide a protective mechanism during stress, prolonged or excessive hyperglycemia can exacerbate inflammation and oxidative stress, contributing to adverse outcomes in conditions such as acute myocardial infarction, heart failure, and cerebrovascular diseases. The stress-hyperglycemia ratio (SHR), defined as the ratio of admission glucose to estimated mean glucose (derived from glycated hemoglobin [HbA1c]), has emerged as a valuable tool for quantifying stress hyperglycemia. Unlike absolute glucose levels, the SHR accounts for background hyperglycemia and provides a more accurate indicator of the relative glucose elevation associated with critical illness. Extensive research has demonstrated a U-shaped or J-shaped relationship of the SHR with disease outcomes, indicating that both low and high SHRs are associated with increased mortality and morbidity. The SHR has shown significant predictive value in cardiovascular diseases (e.g., acute coronary syndrome, heart failure), cerebrovascular diseases (e.g., acute ischemic stroke, intracerebral hemorrhage), and infectious diseases (e.g., sepsis, pneumonia). It also plays a role in other conditions, such as acute pancreatitis and certain cancers. The ease of calculating the SHR from widely available admission glucose and HbA1c tests makes it a practical and valuable prognostic marker in clinical settings. This review examines the relationship between the SHR and critical illnesses, highlighting its mechanisms and predictive value across various diseases.

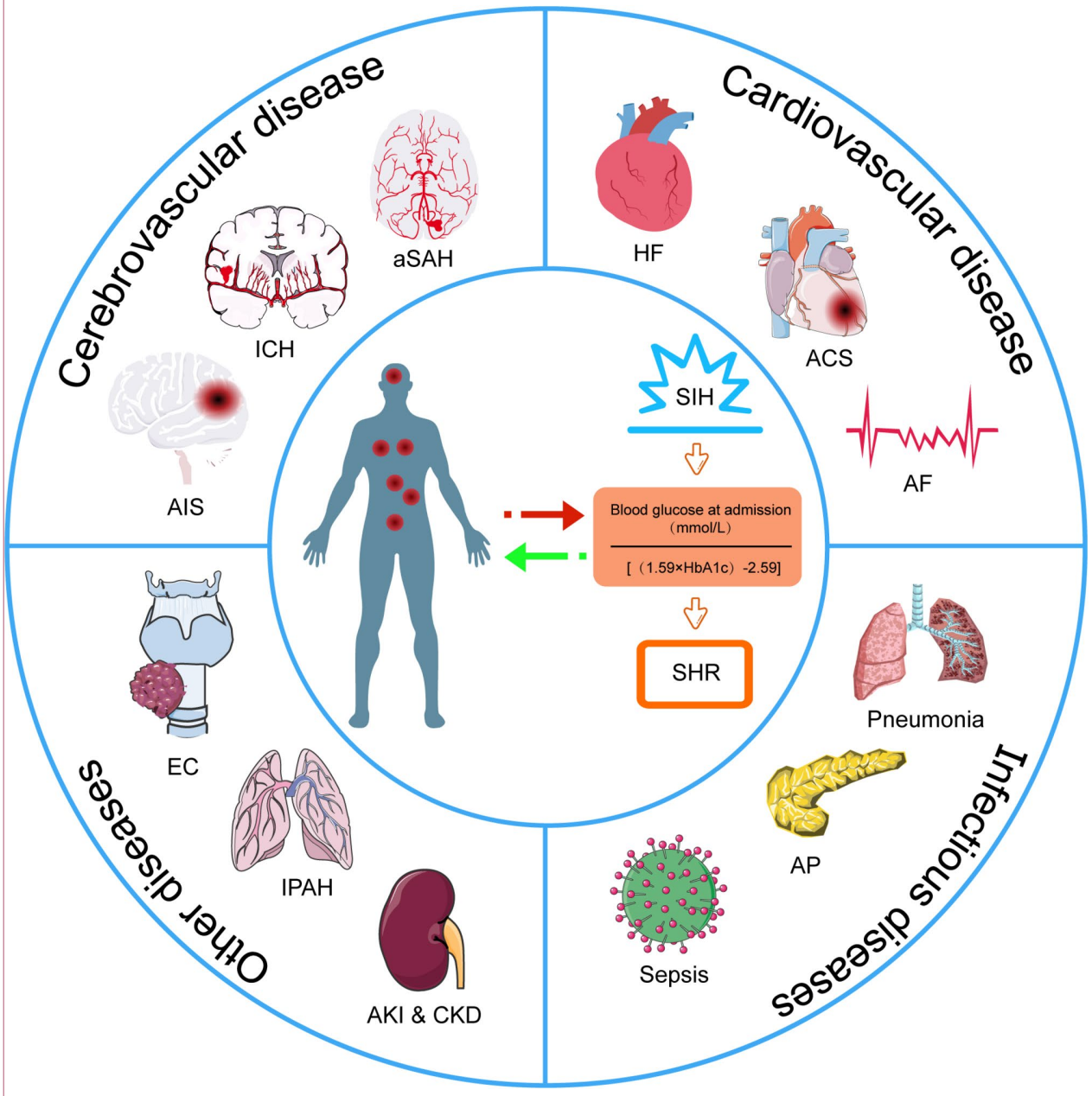
Keywords Stress-hyperglycemia ratio (SHR), Critical illness, Stress-induced hyperglycemia (SIH), Prognostic marker, Insulin resistance, Cardiovascular disease, Cerebrovascular disease

*Correspondence:
Gang Wang
andy_43321@163.com
Fangfang Ma
mafangfang@hebmu.edu.cn

[1]Department of Cardiology, The First Hospital of Hebei Medical University, 89 Donggang Road, Shijiazhuang 050000, Hebei, China
[2]Department of Intensive Care Unit, The First Hospital of Qinhuangdao, 258 Wenhua Road, Qinhuangdao 066000, Hebei, China

Graphical abstract

Predictive value of SHR in cardiovascular, cerebrovascular, infectious, and other diseases.



Research insights

What is currently known about this topic?

- SIH common in critical illness. SHR better than glucose levels. SHR predicts outcomes in majordiseases.

What is the key research question?

- How does the SHR predict outcomes in critical illnesses?

What is new?

- SHR's Ushaped impact on prognosis. SHR's role beyon d glucose levels. SHR guiding multitargeted therapies.

How might this study influence clinical practice?

- SHR could improve risk stratification and guide targeted interventions in critically ill patients.

Introduction

Stress-induced hyperglycemia (SIH) is a condition characterized by elevated blood glucose levels precipitated by either acute or chronic stress. It is not only prevalent among individuals with diabetes but can also be observed in patients without diabetes, particularly in those experiencing acute or critical illnesses [1]. The occurrence of hyperglycemia in response to acute stress is widely regarded as a physiological response mechanism designed to provide the body with increased energy to cope with unexpected events [1]. The development of SIH is contingent upon a multifaceted interplay of counterregulatory hormones, encompassing catecholamines, growth hormones, cortisol, and inflammatory mediators such as cytokines [2, 3]. Feedback and feed-forward loops between these hormones and cytokines have been identified as crucial elements in the development of this response [3]. These loops have been shown to lead to increased hepatic glucose production and insulin resistance [4], resulting in elevated levels of hepatic glucose output. In this context, gluconeogenesis has been identified as a pivotal factor in SIH [5]. However, prolonged or excessive stress hyperglycemia may have detrimental effects on organisms, with hyperglycemia exacerbating cytokine production, inflammation and oxidative stress, which may lead to a vicious cycle in which hyperglycemia leads to further hyperglycemia [6, 7]. This disease process has been associated with the onset, progression and prognosis of a number of diseases of notable importance, including acute myocardial infarction, heart failure, and cerebrovascular diseases [2, 8, 9].

Many studies have shown that SIH is associated with poor outcomes in critically ill patients. However, in the absence of additional evidence, glucose levels are chosen arbitrarily. As a result, the definition of the optimal threshold for SIH is inconsistent across guidelines. The European Society of Cardiology (ESC) recommends defining SIH as an admission glucose level greater than 11 mmol/L (198 mg/dL) *, whereas the American Heart Association (AHA) recommends defining SIH as an admission glucose level greater than 10 mmol/L (180 mg/dL), regardless of the diagnosis of diabetes [10, 11]. Although, hyperglycemia in hospitalized patients is associated with increased mortality in a variety of patient groups, including critically ill patients [12–14]. However, the relationship between glucose concentration and patient prognosis is complex. A number of underlying conditions [15], known diabetes mellitus [16] and background hyperglycemia (i.e., patients with high baseline blood glucose) [17] may influence the association between glucose and patient prognosis. Therefore, the hyperglycemic state of a hospitalized patient may be due to the presence of stress hyperglycemia; it may also reflect poor glycemic control in individuals with chronic diabetes, being similar to that patient's preadmission glucose level, or both. Mortality has subsequently been found to be greater in patients with new-onset hyperglycemia than in patients with known diabetes with hyperglycemia [18, 19]. This finding also suggests that elevated blood glucose due to stress hyperglycemia is a more accurate indicator of disease prognosis than elevated blood glucose in patients with known diabetes and background hyperglycemia [20].

Therefore, to better identify and quantify stress hyperglycemia, in 2015, Roberts et al. first proposed a new parameter to assess stress hyperglycemia, the stress hyperglycemia ratio (SHR), a value calculated by mathematical modeling from immediate admission glucose and glycated hemoglobin (HbA1c) [21]. Nathan et al. developed an equation to convert HbA1c to estimated mean glucose, i.e., estimated mean glucose = (1.59 × HbA1c) − 2.59, which is widely used [22]. The SHR is calculated by dividing admission glucose by estimated mean glucose and is used to define stress hyperglycemia. When both admission glucose and SHR were included in multivariate analyses, elevated relative glucose, as defined by the SHR, was independently associated with critical illness, whereas admission glucose was not. This finding was similar in patients with or without background hyperglycemia, and an increased risk of critical illness was identified in patients with relative hyperglycemia at a glucose concentration of < 10 mmol/L (180 mg/dL) [21]. This has been confirmed in follow-up studies, in which the SHR increased the area under the ROC curve of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [23, 24], and the relationship between the SHR and mortality was not affected by diabetes status [23]. Because admission glucose levels and HbA1c levels are widely available and the SHR is easy to calculate, the SHR is a good quantitative indicator of stress hyperglycemia and is widely used in predicting disease severity.

As research on the SHR has become more extensive, it has become apparent that the SHR plays an important predictive role in many diseases, including cardiovascular diseases, cerebrovascular diseases, infectious diseases, and some other critical diseases [25–30]. A previous study revealed that the relationship between blood

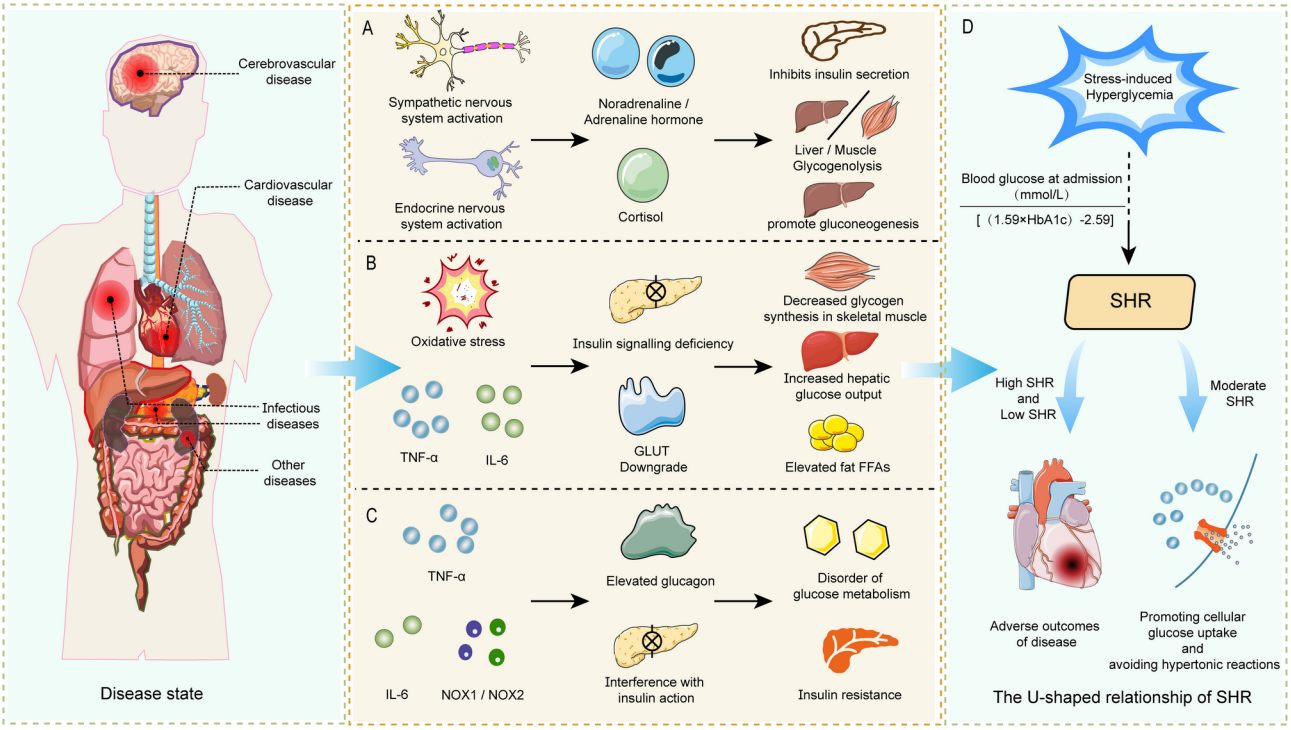


Fig. 1 The mechanism between SIH and diseases. **A** In the disease state, the stress response, through the activation of the sympathetic nervous system and the endocrine system, causes an increase in the secretion of adrenaline, noradrenaline, cortisol, etc. Among them, adrenaline and noradrenaline can promote the breakdown of glycogen in the liver and muscles, releasing glucose into the blood. Cortisol will increase blood glucose levels by promoting gluconeogenesis in the liver. **B** Chronic stress can lead to insulin resistance by upregulating inflammatory factors and oxidative stress levels, resulting in post-receptor insulin signaling defects and downregulation of glucose transporter (GLUT). **C** Inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), NADPH oxidase-2 (NOX2), and NADPH oxidase-1 (NOX1) can disrupt the body's metabolic pathways and interfere with the normal action of insulin, thereby promoting insulin resistance. Tumor necrosis factor-α (TNFα) may promote gluconeogenesis by stimulating the production of glucagon. **D** The U-shaped association between SHR and critically ill patients. Moderate SHR helps optimize cellular glucose uptake while avoiding hyperosmolar reactions. Low and high SHR levels are associated with more adverse disease outcomes and increased mortality. SIH: Stress-induced Hyperglycaemia, SHR: Stress Hyperglycaemia Ratio

glucose and mortality in patients with acute myocardial infarction was 'J' shaped, with an increase in mortality when blood glucose was less than 3.9 mmol/L (70 mg/dL) [31]. With the progress of SHR research, the findings have been similar, with the relationship between the SHR and adverse disease outcomes being mostly 'U' shaped or 'J' shaped[#]. However, the research value of the 'U-shaped relationship' between the SHR and adverse outcomes is also evident, with an increase in adverse outcomes when it reaches a low threshold [32, 33]. This paper reviews the mechanism of the SHR in acute and critical diseases and its clinical significance and summarizes the role and predictive value of the SHR in various diseases.

Mechanisms of occurrence

Stress response and glucose metabolism

In disease states, a combination of factors influences the development of stress hyperglycemia [1]. The stress response is a primary factor in this process, leading to a series of physiological changes through the activation of the sympathetic and endocrine systems. The secretion of stress hormones, including adrenaline, noradrenaline, and cortisol, is increased, and these hormones affect blood glucose levels through different mechanisms. During sympathetic overactivation, catecholamines reduce glucose uptake by peripheral tissues by inhibiting insulin secretion and enhancing glycogenolysis and activating proinflammatory signaling pathways associated with hyperglycemia [34, 35]. Specifically, epinephrine and norepinephrine increase blood glucose levels by stimulating glycogen phosphorylase in the liver and muscle and accelerating glycogen degradation [36]. Furthermore, cortisol has been demonstrated to exacerbate the hyperglycemic state by promoting hepatic gluconeogenesis through upregulating the expression of key enzymes of gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) [37]. (Fig. 1A). The impact of these stress hormones on insulin secretion is a key factor in the overall physiological response, with a decrease in insulin sensitivity resulting in an increase in blood glucose.

Insulin resistance

An important mechanism of stress hyperglycemia is insulin resistance [4], whereby prolonged stress leads to defective postreceptor insulin signaling [38] and the downregulation of glucose transporter proteins (GLUTs) [39] by increasing the levels of inflammatory factors and oxidative stress. Furthermore, the activation of the sympathetic nervous system has been demonstrated to increase the secretion of glucagon, catecholamines, cytokines and cortisol [40, 41]. These mediators stimulate the hepatic release of glucose and mobilization of circulating free fatty acids (FFAs) from adipose tissue, and the increase in FFAs not only causes a dose-dependent inhibition of glucose uptake and myoglycogen synthesis by FFAs [42] but also inhibits glucose entry into the cell through inhibition of glucose transport, leading to insulin resistance [43]. This, in turn, interferes with normal insulin function. The diminished effectiveness of insulin augments the demand of the body for it, thereby increasing blood glucose levels. The resulting impairment in insulin signaling pathways is a well-documented phenomenon, with a strong association with the development of acute stress, particularly in critically ill patients. Additionally, the impaired nonoxidative glucose processing may be attributable to reduced glycogen synthesis in skeletal muscle [44] (Fig. 1B).

Chronic inflammatory response

In certain acute and critical diseases (e.g., sepsis, acute myocardial infarction), the chronic inflammatory response of the body also has a significant effect on blood glucose levels [45]. Inflammatory factors such as tumor necrosis factor-α (TNF-α) [41], interleukin-6 (IL-6) [46], NAPDH oxidase-2 (NOX2), and NAPDH oxidase-1 (NOX1) have been shown to disrupt metabolic pathways [47]. These factors can interfere with the normal action of insulin, promote insulin resistance, and lead to increased blood glucose levels. Furthermore, TNFα may promote gluconeogenesis by stimulating glucagon production [48] (Fig. 1C).

Mechanisms of the U-shaped associations between the SHR and outcomes in critically ill patients

Existing studies have demonstrated a 'U-shaped' relationship between the SHR and clinical outcomes in critically ill patients, suggesting that stress hyperglycemia has dual regulatory properties [32]. A number of clinical observations have demonstrated that mild to moderate stress hyperglycemia (blood glucose levels ranging from 7.8 to 12.2 mmol/L [140 to 220 mg/dL]) has a significant protective effect during periods of acute stress, particularly in cases of ischemic injury [32, 49] (Fig. 1D). The mechanisms by which this occurs may involve the following: First, moderately elevated blood glucose levels during ischemic conditions due to insufficient perfusion significantly increase the efficiency of glucose uptake by tissues by promoting GLUTs membrane localization and establishing a new glucose metabolic homeostasis [49, 50]. Second, as shown in a rat model of myocardial infarction, the upregulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) results in fewer apoptotic cells, reduced infarction size, and improved left ventricular systolic function [50]. Third, moderate osmolarity is maintained to avoid mitochondrial oxidative stress and overactivation of apoptotic signaling pathways triggered by extreme hyperglycemia [51]. Collectively, these findings lend support to the 'physiological adaptation hypothesis' of stress hyperglycemia, which states that the organism possesses the capacity to (i) meet the metabolic needs of tissues in energy crisis; (ii) activate endogenous cytoprotective mechanisms; and (iii) avoid glycotoxicity-induced damage by finely regulating the blood glucose concentration in the critical state. Importantly, this protective effect is concentration dependent; when blood glucose exceeds a certain value, it leads to the conversion of the protective effect to damage [32, 49, 51].

Relationship to disease

Cardiovascular diseases

Coronary artery disease (CAD), particularly acute coronary syndrome (ACS), remains the leading cause of death worldwide [52]. Stress hyperglycemia has been found to be independently associated with poor early and late prognoses in patients with ACS, especially those diagnosed with acute myocardial infarction (AMI) [53, 54]. This may be attributable to the fact that stress hyperglycemia exacerbates acute cardiac disease in several ways, including the exacerbation of microvascular obstruction [55], the attenuation of endothelium-dependent vasodilation [56], the impairment of platelet nitric oxide reactivity [57], and the facilitation of other mechanisms of vascular injury mediated by hyperglycemia. Consequently, the SHR serves as a valuable indicator of stress hyperglycemia and a means to predict adverse outcomes in CAD patients. A large cohort study from Asia revealed that the SHR was independently associated with short- and long-term major adverse cardiovascular events (MACEs) in ACS patients treated with drug-eluting stent (DES) implantation in either a U- or J-shaped relationship, with a significant increase in the incidence of MACEs at an SHR > 0.78 [33]. Subsequent studies have obtained similar results, with elevated SHRs being independently associated with a poor long-term prognosis in ACS patients, regardless of diabetes status. These findings suggest that the SHR is a potential biomarker for risk stratification after ACS [58]. Although the SHR is an independent risk factor for ACS regardless of the

presence of diabetes mellitus, it has also been found that high SHR is more significantly associated with an increased risk of multivessel CAD than with an increased risk of single-vessel CAD, which may be related to the fact that multivessel CAD triggers severe inflammatory infiltration and endothelial dysfunction, leading to more severe glucose and lipid metabolism disturbances. Therefore, the SHR seems to be a predictor of CAD severity [59]. The SHR has also been found to be more predictive in patients with prediabetes mellitus (pre-DM) and diabetes mellitus (DM) [59, 60]. To further confirm the predictive ability of SHR in ACS, a large number of studies have subsequently found that SHR is not only associated with the occurrence of short- and long-term MACEs in patients with AMI, including acute ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris, regardless of whether they undergo percutaneous coronary intervention (PCI) or not [61–63]. Furthermore, the SHR has been identified as a superior biomarker of in-hospital mortality and morbidity [64] and a reliable predictor of the incidence of in-hospital cardiac arrest (IHCA) in patients with ACS treated with PCI [65]. The Global Registry of Acute Coronary Events (GRACE) score is a powerful tool for predicting in-hospital mortality in ACS patients [66], and studies have shown that the SHR, but not the ABG, is an independent predictor of in-hospital mortality in AMI patients, even after adjusting for the GRACE score. The SHR improves the predictability and clinical utility of prognostic models that include the GRACE and Thrombolysis in Myocardial Infarction (TIMI) STEMI score [61, 67]. Moreover, the SHR has been identified as a valuable predictor of adverse outcomes in patients with nonobstructive coronary myocardial infarction (MINOCA) [68, 69], chronic total occlusion (CTO) [70], moderate-to-severe coronary calcification (MSCAC) [71], and coronary triple vascular disease (CTVD) [72]. The value of the SHR in the prediction of adverse outcomes in patients with CAD is evident.

Heart failure (HF) is a clinical condition characterized by cardiac systolic and/or diastolic dysfunction, resulting in inadequate perfusion of peripheral organs and tissues [73]. Increasing evidence suggests that SIH may contribute to an important physiological mechanism for the decline in cardiac function in HF [1, 74] by exacerbating myocardial injury and dysfunction through oxidative stress, inflammatory responses, and vascular endothelial dysfunction [75, 76]. A dramatic increase in plasma glucose levels triggers endothelial dysfunction, oxidative stress and inflammation [77] and activates coagulation [78]. These changes can lead to atherosclerosis [79] and cardiomyopathy [80], impairing myocardial contractility, promoting fluid retention, and exacerbating HF symptoms. Consequently, the utilization of the SHR for the timely identification of stress hyperglycemia is of paramount importance in the prognostication of HF. A meta-analysis reported that SHRs above baseline levels were associated with a poor clinical prognosis in HF patients [81]. Building on these findings, Zhou et al. subsequently demonstrated a U-shaped association between SHR and all-cause death, cardiovascular death, and HF-related rehospitalization in diabetes patients with acute decompensated heart failure (ADHF) [82]. The study indicated that both increased and decreased SHRs were associated with a poor long-term prognosis for both ADHF patients and persons with diabetes. In addition, subsequent studies have shown that an elevated SHR is independently associated with an increased risk of adverse outcomes in heart failure patients with a preserved ejection fraction (HFpEF) compared with patients with a low SHR [83]. Additionally, the adverse effects of hyperglycemia on left ventricular (LV) remodeling and function increase the risk of HF in combination with a number of diseases, including AMI and heart valve disease [84]. Consequently, the value of outcome prediction in HF patients via the SHR is well documented in clinical practice.

Atrial fibrillation (AF) represents a significant challenge within the domain of cardiovascular care, with its incidence exhibiting a consistent increasing trend [85]. Research has revealed a positive correlation between the SHR and all-cause mortality in critically ill patients with AF [86]. Furthermore, the SHR has been identified as a reliable predictor of certain complications associated with various diseases. For example, new-onset atrial fibrillation (NOAF) is a common complication in the acute phase of AMI, and studies have shown that the SHR is an independent predictor of NOAF after AMI, in addition to the neutrophil–lymphocyte ratio (NLR) [87, 88]. A cohort study also revealed that SHR in patients with severe aortic stenosis who underwent transcatheter aortic valve replacement (TAVR) was linearly associated with the risk of all-cause mortality, cardiovascular mortality or readmission for heart failure, and MACEs and that patients with an SHR greater than 0.944 had a poorer prognosis than patients with lower SHRs [89]. Meanwhile, both the lowest and highest fasting SHRs were significantly associated with an increased incidence of contrast-induced acute kidney injury (CI-AKI) in those undergoing coronary angiography (CAG) or PCI [71]. Collectively, these factors can induce a series of deleterious changes within renal tissues, ultimately culminating in renal dysfunction and increased susceptibility to CI-AKI [90, 91]. Furthermore, an elevated SHR has been identified as a substantial predictive risk factor for the occurrence of ventricular arrhythmia (VA) in critically ill patients admitted to the intensive care unit (ICU) [92]. Similarly, in patients with cardiogenic shock (CS), stress hyperglycemia, as measured by the SHR, has been shown

to be a strong predictor of ICU mortality [93]. In cardiac ICU, a U-shaped association was observed between the SHR and short-term mortality in cardiac ICU patients [63].

In conclusion, the SHR is a significant predictor in the domain of cardiovascular medicine, playing a pivotal role in the diagnosis, treatment and prognosis of cardiovascular diseases. Given the critical nature of cardiac diseases, it is imperative to develop a comprehensive understanding of the correlation between SHR and clinical outcomes. These findings may facilitate the early identification of high-risk patients and inform the development of effective interventions to improve patient prognosis.

Cerebrovascular diseases

Stroke is defined as a disease in which damage to the cerebral vasculature occurs from a variety of causes, resulting in focal or overall damage to brain tissue [9]. It is the leading cause of death worldwide. Of these, acute ischemic stroke (AIS) accounts for 60–70% of all strokes [94], with high mortality and disability rates. Research has demonstrated that the metabolic status of patients at the time of admission is associated with the exacerbation of AIS [95], and persistent hyperglycemia is an independent risk factor for infarct expansion [96]. SIH has been identified as a significant factor contributing to the exacerbation of stroke complications and the enhancement of unfavorable prognoses [97]. The mechanisms underlying the prognostic association of stress hyperglycemia in patients with AIS have not been thoroughly investigated but may be related to the following mechanisms. SIH reflects greater disease severity and triggers a heightened inflammatory response, promoting neuroinflammation and vascular endothelial damage through released vascular factors [1]. Acute glucose fluctuations exacerbate endothelial dysfunction and oxidative stress [98]. Additionally, anaerobic glucose metabolism in hyperglycemic conditions elevates lactic acid, causing cellular acidosis that accelerates brain injury [1]. Hyperglycemia also induces inflammation, oxidative stress, and matrix metalloproteinase-9 activation, disrupting the blood–brain barrier and worsening cerebral edema [99, 100]. Finally, hyperglycemia enhances platelet activation, promoting abnormal aggregation that further aggravates the condition [26]. The SHR is associated with increased short- and long-term mortality in patients with AIS, independent of diabetes status [101, 102]. A meta-analysis encompassing 11 cohort studies further suggested that an elevated SHR is associated with unfavorable outcomes in AIS patients and that the SHR may serve as a novel predictor of a poor prognosis in AIS patients [103]. Merlino et al. demonstrated that stress hyperglycemia was associated with a poor prognosis in patients with acute ischemic stroke following intravenous thrombolysis in a study of 414 patients (excluding diabetes status) and that there was a significant trend in the quartiles of the SHR toward a poor prognosis and mortality [104]. Meanwhile, SHR was independently associated with mortality outcomes in patients with AIS treated with recombinant tissue plasminogen activator (rt-PA). This finding indicates that the SHR has a superior ability to predict other glucose indicators [105]. The presence of the SHR at admission has been demonstrated to be associated with an elevated risk of hemorrhagic conversion in patients with AIS [26]. Consequently, these studies have confirmed the prognostic value of the SHR in patients with AIS.

Intracerebral hemorrhage (ICH) is the second most prevalent subtype of stroke, with a poor prognosis and high mortality rate, including a 30-day mortality rate of up to 40% [106]. Despite ongoing efforts, the number of effective treatments for ICH remains limited in comparison to those available for ischemic stroke [107]. Consequently, early determination of ICH prognosis is highly important in clinical practice. A substantial body of previous research has indicated that stress hyperglycemia is associated with an elevated risk of death and an unfavorable functional prognosis following ICH [14]. However, in most previous studies, stress hyperglycemia has been defined as absolute hyperglycemia on the basis of random or fasting blood glucose levels, without excluding the effect of chronic background hyperglycemia [14, 108]. The SHR has been instrumental in enabling effective differentiation between SIH and diabetic hyperglycemia. A two-center prospective study and subsequent research have consistently shown that the SHR is strongly associated with hematoma enlargement, a poor prognosis, and in-hospital mortality in ICH patients, suggesting its potential as a useful adjunct indicator for in-hospital prognosis in cerebral hemorrhage patients [109, 110]. Additionally, the SHR has been identified as a predictor of ICU length of stay following minimally invasive surgery (MIS) in ICH patients, offering clinicians a more precise understanding of recovery expectations [111].

Subarachnoid hemorrhage (SAH) resulting from the rupture of intracranial aneurysms, despite constituting a mere 5% of all stroke cases, is associated with a mortality rate that exceeds one-third within days to weeks following the onset of symptoms [112]. A significant association was identified between the SHR and the incidence of a poor functional prognosis in patients with SAH, independent of diabetes status [113], a finding that emphasizes the importance of the SHR as a prognostic indicator for SAH patients. Acute basilar artery occlusion (ABAO) is a rare but catastrophic type of stroke that accounts for 1% of all ischemic strokes, but approximately 68% of patients die or survive with severe disability [114]. Some studies have shown that the SHR is associated with a reduced likelihood of a good functional prognosis at 90 days and

1 year after endovascular therapy (EVT) in patients with ABAO [115]. Meanwhile, the SHR has been identified as an independent predictor of early neurological deterioration (END) and an unfavorable prognosis in patients with a single subcortical infarct (SSI), particularly among elderly patients and those with a proximal SSI [116]. The findings of these studies underscore the clinical significance of the SHR in cerebrovascular disease and provide significant insights that could inform the optimization of personalized risk assessment strategies, the guidance of targeted interventions, and the investigation of the optimal blood glucose range in patients with cerebrovascular disease, as well as the formulation of targeted glucose-lowering strategies.

Infectious diseases

Sepsis is defined as a life-threatening organ dysfunction syndrome triggered by a dysregulated host immune response to infection and is most commonly observed in patients with severe trauma or serious infections. Its pathophysiology is characterized by an uncontrolled systemic inflammatory response, which often progresses to multiple organ dysfunction syndrome (MODS), with very high morbidity and mortality rates [117]. Sepsis is associated with an unacceptably high mortality rate of more than 35% at 90 days [118]. Consequently, researchers and clinicians are continually exploring the various factors that contribute to the outcomes of sepsis, with a particular focus on identifying markers and predictors of mortality [119]. Early identification of high-risk patients susceptible to sepsis is imperative to prevent this condition and reduce the disease burden. SIH plays a significant role in sepsis, with some studies confirming the prognostic value of SIH in sepsis [120]. The mechanism may involve elevated blood glucose in SIH, which promotes monocyte/macrophage aggregation and the release of inflammatory cytokines (e.g., IL-6, IL-8), contributing to inflammation and tissue damage [121]. Acute glucose spikes also impair endothelial function, potentially triggering abnormal coagulation and sepsis-associated disseminated intravascular coagulation (DIC) [122]. Additionally, stress hyperglycemia increases mitochondrial ROS production in endothelial cells, worsening endothelial dysfunction [123]. Sepsis further aggravates hyperglycemia by activating the HPA axis, causing hormonal secretion and insulin suppression [124]. This sequence of events can result in a positive feedback loop, contributing to an increased risk of mortality in septic patients. Research has shown that the SHR has a U-shaped relationship with mortality in septic patients, where both low and high values predict worse outcomes, making it a potential prognostic marker for critically ill septic patients [125, 126]. When heart failure is combined with sepsis, there is sepsis-induced myocardial dysfunction and a systemic inflammatory response that exacerbates heart failure symptoms and increases the risk of adverse outcomes, and a cohort study found that the SHR was an independent prognostic factor in patients with heart failure combined with sepsis [29]. This finding underscores the importance of the SHR in patients with sepsis, and monitoring the SHR could serve as a valuable way for clinicians to identify patients at high risk of sepsis and facilitate timely clinical interventions.

Pneumonia is one of the leading causes of morbidity and mortality worldwide. Hospital-acquired pneumonia (HAP) is defined as inflammation of the lung parenchyma that does not exist and is not in the incubation phase of infection at the time of admission to the hospital but occurs 48 h or more after admission [127]. The presence of SIH in hospitalized patients has been found to be strongly associated with an increased rate of infection [128, 129], thus underscoring the importance of the early recognition of SIH and glycemic control in reducing HAP. In 2023, Roberts et al. conducted a study of HAP, in which they defined SIH on admission by an SHR ≥ 1.1 as opposed to by conventional markers such as blood glucose ≥ 10 mmol/L (180 mg/dL). Their findings revealed that the SHR was independently associated with subsequent episodes of HAP, whereas blood glucose was not [28]. Community-acquired pneumonia (CAP) is a significant health concern for elderly individuals, with a mortality rate of 25–50% in severe community acquired pneumonia (SCAP) [130]. SIH has been demonstrated to result in impaired lung function, decreased oxygenation capacity, impeded infection control, and prolonged hospitalization, leading to increased mortality [49]. A cohort study revealed that an elevated SHR, a well-recognized indicator of stress hyperglycemia, is a significant risk factor for death in elderly SCAP patients, irrespective of the presence of diabetes [131]. These findings underscore the pivotal role of the SHR in the prediction of pneumonia outcomes.

The novel coronavirus infection, otherwise known as coronavirus disease 2019 (COVID-19), is an acute infectious disease caused by a novel coronavirus, namely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [132]. The bidirectional relationship between the two conditions has been well documented by previous studies. Diabetes mellitus has been shown to increase the risk of death in patients with novel coronavirus infection, while the novel coronavirus affects β-cells via the angiotensin-converting enzyme 2 (ACE2)-mediated pathway and leads to a surge in a variety of proinflammatory cytokines, resulting in transient hyperglycemia and new-onset diabetes. In some cases, this has been observed to progress to ketosis [133]. A study by Fadini et al. demonstrated that respiratory function deteriorated

Table 1 Predictive value of SHR in different diseases

Disease type	Types of adverse outcomes	Relation	The threshold value for the occurrence of adverse outcomes	References
Cardiovascular disease				
CAD	In-hospital death	J-shaped	> 1.2	Xu et al. [25]
ACS	MACE	J-shaped	> 0.78	Yang et al. [33]
ACS	In-hospital cardiac arrest	J-shaped	> 1.773	Li et al. [65]
AMI	NOAF	--	> 1.119	Luo et al. [87]
STEMI	MACCE	J-shaped	> 1.2	Wei et al. [62]
NSTEMI	All-cause death	--	> 1.53 (DM) > 1.27 (Non-DM)	Sia et al. [34]
Patients with AMI admitted to the ICU	All-cause death	J-shaped	> 1.04	Liu et al. [54]
MINOCA	MACE	--	> 0.86	Abdu et al. [69]
CTVD	Cardiovascular death	J-shaped	< 0.75 or > 1.0	Zhang et al. [60]
MSCAC	MACCE	J-shaped	> 0.83	Lin et al. [71]
HF	MACE	--	> 1.05	Li et al. [81]
ADHF	All-cause death	U-shaped	< 0.64 or > 0.77	Zhou et al. [82]
HFpEF	All-cause deaths, cardiovascular deaths and HF readmission	U-shaped	< 0.74 or > 0.98	Mohammed et al. [83]
CS	ICU mortality rate	U-shaped	< 0.953 or > 1.668	Tian et al. [93]
AF	All-cause death	U-shaped	> 0.73	Cheng et al. [86]
Critically ill patients admitted to the ICU	VA	J-shaped	> 1.31	Shen et al. [92]
Cardiac ICU	Short-term mortality	U-shaped	< 0.75 or > 0.95	Li et al. [63]
Cerebrovascular diseases				
AIS	All-cause death	J-shaped	> 1.02	Zhang et al. [102]
ICH	In-hospital deaths and hematoma expansion	--	> 1.26	Zhang et al. [109]
SAH	Use of the mRS is rated on a scale of 3 to 6	J-shaped	> 1.59	Yang et al. [113]
ABAO	Adverse Functional Outcomes at 90 Days and 1 Year After EVT	--	> 1.37	Peng et al. [115]
SSI	Early deterioration of END	--	> 1.11	Liu et al. [116]
Infectious diseases				
COVID-19	In-hospital death	--	> 1.14	Mondal et al. [135]
CAP	All-cause death	--	> 1.2	Miao et al. [131]
HAP	Incidence rate	--	> 1.1	Roberts et al. [28]
Sepsis	One-year all-cause mortality rate	U-shaped	< 0.75 or > 0.99	Li et al. [126]
HF complicated with sepsis	All-cause death	U-shaped	< 0.7 or > 1.08	Song et al. [29]
Other				
DM or pre-DM	All-cause mortality	J-shaped	> 0.93	Ding et al. [134]
Esophagectomy was performed for EC	30/90 day all-cause deaths	--	> 1.14	Xia et al. [138]
CKD	One-year all-cause	U-shaped	< 0.7 or > 0.95	An et al. [142]
IPAH	Long-term adverse outcomes	J-shaped	--	Zhang et al. [140]
Psoriasis	All-cause mortality	U-shaped	> 1.045	Tuersun et al. [141]
Critical illness	Death and transfer to the ICU	J-shaped	> 1.14	Roberts et al. [21]
Critical illness	All-cause death	U-shaped	< 0.75 or > 0.96	Li et al. [32]

CAD: Coronary artery disease, ACS: Acute coronary syndrome, AMI: Acute Myocardial Infarction, MACE: Major adverse cardiovascular events, MACCE: Major Adverse Cardiovascular and Cerebrovascular Events, NOAF: New- onset atrial fibrillation, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-segment elevation myocardial infarction, ICU: Intensive care units, MINOCA: Moderate-to-severe coronary calcification, CTVD: Coronary triple vascular disease, MSCAC: Moderate-to-severe coronary calcification, HF: Heart failure, ADHF: Acute decompensated heart failure, HFpEF: Heart failure patients with a preserved ejection fraction, CS: Cardiogenic Shock, AF: Atrial fibrillation, VA: Ventricular arrhythmia, AIS: Acute ischemic stroke, ICH: Intracerebral hemorrhage, SAH: Subarachnoid hemorrhage, mRS: modified Rankin Scale, ABAO: Acute basilar artery occlusion, EVT: Endovascular therapy, SSI: Single subcortical infarct, END: Early neurological deterioration, COVID-19: Coronavirus disease 2019, CAP: Community-acquired pneumonia, HAP: Hospital-acquired pneumonia, DM: Diabetes mellitus, pre-DM: Prediabetes mellitus, Non-DM: Non-Diabetes mellitus, EC: Esophageal cancer, CKD: Chronic kidney disease, IPAH: Idiopathic pulmonary arterial hypertension

rapidly in patients with newly diagnosed diabetes and/or hyperglycemia on admission and that patients with confirmed cases of COVID-19 had a worse prognosis than patients with known diabetes did [134]. And SHR may be a more appropriate biomarker for predicting poor prognosis in patients with moderate to severe COVID-19. For example, a cohort study showed that SHR was a better predictor of mortality and poor prognosis in COVID-19 patients than ABG, regardless of prior chronic glycaemic status [135]. Acute pancreatitis (AP) is an autodigestive disease of the pancreatic tissue caused by the abnormal activation of pancreatic enzymes and potentially triggering dysfunction of other organs [136]. Numerous studies have indicated that stress hyperglycemia may be associated with an elevated risk of morbidity and mortality in patients with acute pancreatitis [27]. Bacteremia is a serious condition caused by the presence of an active infectious agent in the body [137], and hospitalized patients with bacteremia suffering from transient stress hyperglycemia are at a greater risk of subsequently developing diabetes mellitus than those with normal blood glucose [30]. Consequently, the critical impact of the SHR on clinical outcomes as an important predictor of potentially altered infectious disease outcomes emphasizes its importance in disease prognosis prediction. The effective management of SHRs through rigorous glycemic control and meticulous monitoring has the potential to improve the prognosis of patients afflicted by infectious diseases.

Others

In addition to the preceding discussion of the pivotal function of the SHR in cardiovascular, cerebrovascular, and infectious diseases, a number of studies have identified the SHR as a key player in other diseases. For example, a study by Xia et al. revealed that among patients admitted to the intensive care unit for serious complications after esophagectomy for esophageal cancer (EC), relative elevations in blood glucose quantified by the SHR were associated with 30/90-day all-cause mortality, whereas absolute hyperglycemia was not, and an SHR ≥ 1.14 could be used to identify people at increased risk of a poor prognosis, especially diabetes [138]. Song et al. reported that both lower and higher SHRs were associated with an increased risk of delirium in older hospitalized patients and that the SHR may be a promising marker for identifying patients at a greater risk of delirium [139]. Other studies in SHR have shown significant associations with idiopathic pulmonary arterial hypertension (IPAH), risk of death in patients with psoriasis (optimal threshold 1.045) and poor prognosis in patients with DM, pre-DM, acute kidney injury (AKI) and chronic kidney disease (CKD) [71, 140–143].

Conclusion

Stress responses, including stress hyperglycemia, have been observed in humans during periods of stress. These responses are primarily mediated by the hypothalamic–pituitary–adrenal axis and the sympathoadrenal system [49]. A substantial body of research has demonstrated that mild to moderate stress hyperglycemia functions as a protective factor during periods of stress, particularly in cases of ischemia. For example, in animal models, stress hyperglycemia has been shown to increase cardiac output and improve survival [33]. Furthermore, in ischemic cells, moderate stress hyperglycemia has been shown to promote more efficient glucose utilization [50]. The SHR, a well-recognized indicator of stress hyperglycemia, has also been extensively documented in its U- and J-shaped relationship with numerous critical illnesses [49]. Admission glucose levels and HbA1c tests are widely available, and the SHR is easily calculable (The relationship between various diseases and SHR is summarised in Table 1). Consequently, the SHR is more valuable than glucose levels alone in predicting critical illness and is widely used [20, 109, 135]. However, it is important to note that HbA1c levels can be affected by various factors, including underlying conditions such as alcoholism, iron deficiency anemia, and hyperlipidemia. These conditions can lead to elevated HbA1c test values [144, 145]. Conversely, patients suffering from hemolytic anemia, those with chronic renal failure or pregnant women with an increased blood volume may exhibit low HbA1c values [146, 147]. Consequently, in the presence of these diseases, consideration should be given to the potential for bias in the calculation of HbA1c, which may be influenced by inaccurate data.

In principle, the regulation of the SHR at a specific level through insulin therapy could offer significant benefits for a wide range of diseases. However, this hypothesis has not been substantiated, and one study reported that insulin basal therapy did not reduce mortality after AMI [148]. One potential explanation for this finding is that stress hyperglycemia is an epiphenomenon of pancreatic β-cell dysfunction, adrenergic and renin-angiotensin-aldosterone system (RAAS) overactivity, hyperglucagonemia, and increased saturated fatty acids [149]. Conversely, the risk of hypoglycemia induced by the use of intensive glucose-lowering therapy can lead to acute glycemic variability, which has been demonstrated to have deleterious effects on prognosis, including long-term effects on cardiovascular outcomes. Consequently, ensuring the maintenance of blood glucose within a safe range while concomitantly ameliorating adverse outcomes by diminishing short-term glycemic variability due to hypoglycemic risk is imperative [47]. Therefore, in addition to insulin therapy, the current use of multi-target therapeutic regimens may be a better option for

controlling stress hyperglycemia. For example, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2is) have been demonstrated to possess cardioprotective properties without the risk of hypoglycemia [45, 47]. However, studies related to GLP-1RAs or SGLT2is in the treatment of SIH are scarce, and whether their potential side effects (e.g., SGLT2i-induced infections and ketoacidosis, glucagon-like peptide-1-associated delayed gastric emptying, and the risk of pulmonary aspiration) have an impact on adverse outcomes remains to be elucidated. Further studies are needed to determine the safety profile. We look forward to the emergence of large controlled studies in the future to confirm the role of the SHR in treatment. Although there is a lack of valid arguments for the precise treatment of stress hyperglycemia, accurate identification of patients with stress hyperglycemia is clinically important for clinicians to judge the prognosis of the disease. The SHR may help to differentiate true blood glucose elevation, which is of clinical interest for assisting clinicians in deciding whether to start glucose-lowering therapy.

Abbreviations

ABAO	Acute basilar artery occlusion
ACE2	Angiotensin-converting enzyme 2
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AHA	American Heart Association
AIS	Acute ischemic stroke
AKI	Acute kidney injury
AMI	Acute Myocardial Infarction
AP	Acute pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II
CAD	Coronary artery disease
CAG	Coronary angiography
CAP	Community-acquired pneumonia
CI-AKI	Contrast- induced acute kidney injury
CKD	Chronic kidney disease
COVID-19	Coronavirus disease 2019
CS	Cardiogenic Shock
CTO	Chronic total occlusion
CTVD	Coronary triple vascular disease
DES	Drug-eluting stent
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
EC	Esophageal cancer
END	Early neurological deterioration
ESC	European Society of Cardiology
EVT	Endovascular therapy
FFAs	Free fatty acids
G6Pase	Glucose-6-phosphatase
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
GLUTs	Glucose transporter proteins
GRACE	Global Registry of Acute Coronary Events
HAP	Hospital-acquired pneumonia
HbA1c	Glycated hemoglobin
HF	Heart failure
HFpEF	Heart failure patients with a preserved ejection fraction
HIF-1α	Hypoxia-inducible factor-1α
ICH	Intracerebral hemorrhage
ICU	Intensive care units
IHCA	In-hospital cardiac arrest
IL-6	Interleukin-6
IPAH	Idiopathic pulmonary arterial hypertension
LV	Left ventricular
MACEs	Major adverse cardiovascular events
MINOCA	Moderate-to-severe coronary calcification
MIS	Minimally invasive surgery
MODS	multiple organ dysfunction syndrome
MSCAC	Moderate-to-severe coronary calcification
NLR	Neutrophil–lymphocyte ratio
NOAF	New- onset atrial fibrillation
NOX1	NAPDH oxidase-1
NOX2	NAPDH oxidase-2
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PEPCK	Phosphoenolpyruvate carboxykinase
pre-DM	Prediabetes mellitus
RAAS	Renin-angiotensin-aldosterone system
rt-PA	Recombinant tissue plasminogen activator
SAH	Subarachnoid hemorrhage
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCAP	Severe community acquired pneumonia
SGLT2is	Sodium-glucose cotransporter 2 inhibitors
SHR	Stress-hyperglycemia ratio
SIH	Stress-induced hyperglycemia
SSI	Single subcortical infarct
STEMI	ST-segment elevation myocardial infarction
TAVR	Transcatheter aortic valve replacement
TIMI	Thrombolysis in myocardial infarction
TNF-α	Tumor necrosis factor-α
VA	Ventricular arrhythmia
VEGF	Vascular endothelial growth factor
#	The U-shaped relationship is characterised by an increase in risk or effect at both low and high levels, with the lowest risk occurring at intermediate levels. The graphical representation of this relationship typically assumes the form of a symmetrical or nearly symmetrical 'U' shaped curve.The definition of the J-shaped relationship involves an asymmetrical variant of the U-shaped relationship, characterised by a more pronounced effect at either low or high levels. The graphical representation of the J-shaped relationship is characterised by a shape resembling the letter 'J' (or its reverse), with a steeper slope on one side
*	The units of blood glucose in this article use the International Organisation for Standardisation (ISO) standard of mmol/L, with the default clinical conversion ratio of 1 mmol/L = 18 mg/dL (rounded to simplified values) in accordance with American Diabetes Association (ADA) guidelines

Acknowledgements
Not applicable.

Author contributions
L.H. and G.J. and L.G. were involved in the conception of this work, C.X. and L.Y. collected the literature, S.G. collated the literature and completed the first draft and drawings, L.X. and W.G. and M.F. made suggestions and revisions to the first draft. All authors reviewed the manuscript.

Funding
This work was supported by the Hebei Province Finance Department Project [ZF2023022] and Key Science and Medical Science Research Projectof Hebei [20230988]; and Natural Science Foundation of Hebei Province [H2024206123].

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Consent for publication
All participants should appear in the manuscript.

Competing interests
The authors declare no competing interests.

Received: 28 February 2025 / Accepted: 21 April 2025
Published online: 02 May 2025

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