International Journal of Clinical Medicine & Pharmacology

https://doi.org/10.70731/mxep4578

Biomarkers of Cardiogenic Shock: Classic Cornerstone and Innovative Frontier

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KEYWORDS

Cardiogenic Shock; Biomarkers; Mechanisms; Clinical Application

ABSTRACT

Cardiogenic shock (CS) is one of the most fatal syndromes among cardiovascular critical conditions. With the advancement of biomarker research, the combination of traditional and emerging biomarkers has significantly improved the early diagnosis, risk stratification, and treatment monitoring of CS. This article provides a systematic review of biomarkers that hold significant value in current clinical practice and explores their pathophysiological mechanisms and clinical application prospects.

Introduction

Cardiogenic shock (CS) is a high-mortality clinical syndrome characterized by a significant decline in cardiac output and inadequate tissue perfusion. Its pathophysiological mechanisms involve myocardial injury, inflammation activation, neuroendocrine disruption, and multi-organ dysfunction [1]. Some biomarkers have been widely applied in clinical practice, providing significant assistance in the early prediction and confirmation of heart failure, myocardial ischemia, or inflammatory responses, thus aiding in the determination of the presence and severity of CS. In recent years, biomarker research has expanded from traditional myocardial injury markers to include inflammation, metabolism, and novel molecular targets, providing important evidence for the early diagnosis, risk stratification, and optimization of treatment strategies for CS. This article aims to systematically review the research progress and potential applications of both classic and emerging biomarkers.

Classic Biomarkers

Classic Markers of Myocardial Injury

Cardiac troponins (cTn) are key regulatory proteins of striated muscle contraction, consisting primarily of three subunits: cTnC, cTnI, and cTnT [2, 3]. In the event of acute myocardial infarction (AMI), cTnI and cTnT are rapidly released from the cytoplasm of myocardial cells into the bloodstream, with levels detectable 3-6 hours post-AMI and remaining elevated for up to two weeks [4]. Since the initial qualitative detection of troponins via ELISA, the advent of chemiluminescence and immunofluorescence methods has reduced the lower detection limit of cTn to 0.014 μg/L (high-sensitivity cTn) [5]. Notably, cTn is not only associated with AMI but is also commonly found in conditions involving impaired cardiac function, such as myocarditis and heart failure, and may also occur in other organ dysfunctions, including pulmonary embolism, renal insufficiency, and sepsis [6]. Current guidelines and expert consensus recommend cTn as the preferred biomarker for AMI, with persistently elevated cTn levels suggesting myocardial ischemia

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Received 5 April 2025; Received in revised form 20 April 2025; Accepted 28 April 2025; Available online 30 April 2025.

(Class I recommendation, Level A evidence) [7]. After excluding causes such as heart failure and renal insufficiency, persistently elevated cTn with a change of less than 20% suggests chronic myocardial injury, while a dynamic change exceeding 20% indicates acute injury [7]. AMI is one of the primary causes of CS, and combining cTn with electrocardiography and imaging can rapidly clarify the etiology of CS (Class I recommendation, Level B evidence) [8]; continuous monitoring of cTn levels can objectively reflect myocardial recovery (Class IIa recommendation, Level B evidence) [9]. Currently, the application of cTn in CS largely depends on clinical judgment, and further research is needed to explore evidence-based management of cTn in CS applications [10].

Creatine kinase (CK) and its isoenzymes are important biomarkers in the clinical diagnosis of CS. Due to the high sensitivity of CK concentration and its susceptibility to interference from factors such as skeletal muscle injury, renal insufficiency, and hemolysis, CK isoenzymes are preferred for diagnosing and assessing the prognosis of CS [11, 12]. The CK isoenzymes mainly include three subtypes: MM, MB, and BB, with CK-MB being the myocardium-specific isoenzyme. It is present in very low amounts in skeletal muscle, and its concentration is less influenced by skeletal muscle injury, making it highly specific and recommended as the "gold standard" for diagnosing AMI (Class I recommendation, Level A evidence) [13, 14]. Elevated CK-MB levels are positively correlated with the infarction area in AMI. However, for patients with recurrent myocardial infarction, the diagnostic value of CK-MB is extremely limited due to its short half-life, and its use should be combined with cardiac troponin (cTn) to improve diagnostic sensitivity and specificity [15, 16]. In addition to the three subtypes (MM, MB, and BB), mitochondrial-type CK (CK-Mt) has been reported to play a role in the progression of CS. When myocardial cells undergo ischemia-reperfusion injury, leading to increased mitochondrial membrane permeability, CK-Mt blood concentration may rise significantly, suggesting that CK-Mt has potential as a biomarker for CS [17, 18]. However, to date, there is limited research on this, and the existing literature does not explicitly indicate that CK-Mt can be used as an independent marker for CS diagnosis or assessment.

In CS, tissue hypoperfusion leads to enhanced anaerobic metabolism and increased lactate production [19]. As a key enzyme in lactate metabolism, lactate dehydrogenase (LDH) is released into the bloodstream from damaged myocardial cells during myocardial ischemia. The peak blood concentration of LDH after AMI occurs between 48 and 72 hours, which is useful for assisting diagnosis in patients who seek medical attention late (Class IIa recommendation, Level B evidence) [20]. The peak levels of LDH have been shown to be positively correlated with the infarct size, and continuous monitoring of LDH can assess myocardial injury progression and reperfusion status (Class IIb recommendation, Level B evidence) [21]. LDH lacks tissue specificity, and its levels can be elevated in cases of skeletal muscle injury, liver disease, hemolysis, tumors, and other conditions, making its standalone use in diagnosing CS limited [22]. Combining LDH with other biomarkers for a joint diagnosis is beneficial in improving the diagnostic accuracy of CS. Multicenter randomized controlled trials have shown that combining LDH with cardiac troponin (cTn) or CK-MB for monitoring enhances the sensitivity of diagnosing myocardial injury (Class IIa recommendation, Level B evidence) [23]. To date, the evidence for the application of LDH in CS is primarily based on observational data, with a lack of high-quality randomized controlled trials. Furthermore, it remains of significant research value to validate the relationship between dynamic changes in LDH and CS risk stratification treatment.

Classic Cardiac Function Markers

B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) are important biomarkers of heart failure [24]. BNP/NT-proBNP levels are significantly elevated during myocardial ischemia, necrosis, or increased ventricular wall tension. The peak levels of BNP/NT-proBNP after AMI can predict the risk of left ventricular remodeling, heart failure, and mortality, with predictive value even superior to traditional echocardiography (Class IIa recommendation, Level B evidence) [25]. Elevated BNP/NT-proBNP levels are associated with left and right ventricular dysfunction in CS patients. Persistently high levels of BNP/NT-proBNP (e.g., NT-proBNP > 1000 pg/mL) are independently correlated with mortality in CS patients, while a decrease in levels by ≥30% after treatment suggests treatment efficacy (Class IIa recommendation, Level B evidence) [26-28]. Similarly, the evidence for the application of BNP/NT-proBNP in CS primarily comes from observational studies, with a lack of validation through randomized controlled trials. Moreover, its specificity is lower due to interference from factors such as renal dysfunction, advanced age, and atrial fibrillation.

Heart-type fatty acid-binding protein (H-FABP) is a small molecular cytosolic protein predominantly expressed in cardiomyocytes, constituting 4%-8% of the total protein in the myocardium. It provides 60%-90% of the energy for the myocardium by binding and transporting free fatty acids [29]. H-FABP can be detected in the blood within 1-3 hours after the onset of AMI, reaching its peak levels at 6-8 hours, and returning to baseline levels within 24-30 hours [30]. The diagnostic sensitivity of H-FABP is significantly superior to that of cardiac troponin I (cTnI), especially within 3 hours following the onset of chest pain, where its negative predictive value for excluding AMI approaches 100% (Class IIa recommendation, Level B evidence) [30, 31]. Persistently elevated H-FABP levels (>8.8 ng/mL) are independently associated with short-term (150-day) mortality in patients with CS, with a mortality risk approximately 3.25

times higher in patients with high H-FABP levels compared to those with low levels (Class IIa recommendation, Level B evidence) [32]. H-FABP is also expressed in small amounts in skeletal muscle and the kidneys, and renal dysfunction or muscle injury may lead to false positives [33]. Furthermore, the diagnostic window for H-FABP in CS is short, as levels return to normal in most patients within 24 hours, necessitating the use of additional biomarkers to enhance diagnostic continuity [34].

Soluble suppression of tumorigenicity 2 (sST2) is a key biomarker reflecting myocardial fibrosis and ventricular remodeling [35]. Studies have shown that sST2 levels are significantly elevated in patients with AMI, and its levels are positively correlated with the risk of left ventricular remodeling, making it a potential monitoring marker for the progression of fibrosis after myocardial injury (Class IIa recommendation, Level B evidence) [36]. Persistent elevation of sST2 (>35 ng/mL) is associated with a more than threefold increased short-term mortality risk in patients with CS (Class IIa recommendation, Level B evidence) [37, 38]. Small-scale studies have indicated that a decrease in sST2 levels after active treatment correlates with the efficacy of β-blockers and ACE inhibitors/ARBs, with a reduction of ≥30% suggesting a good treatment response (Class IIb recommendation, Level C evidence) [39]. The diagnostic specificity of sST2 is high, unaffected by factors such as age, BMI, renal function, or atrial fibrillation, and its combined use with other high-sensitivity biomarkers in diagnosing CS improves diagnostic accuracy.

Classic Inflammatory Markers

Myocardial ischemia is one of the major causes of CS, and the inflammation induced by ischemia-reperfusion further exacerbates the patient's condition. Therefore, several studies have explored the application of inflammatory biomarkers in the diagnosis and treatment of CS. Research shows that elevated C-reactive protein (CRP) is positively correlated with the risk of left ventricular remodeling, heart failure, and reduced left ventricular ejection fraction [40]. Persistent elevation of CRP indicates an exacerbation of systemic inflammation and microcirculatory dysfunction, serving as an independent risk factor for short-term mortality in CS patients [41]. Interleukin-6 (IL-6) significantly increases within 6 hours after AMI, peaking at 3 days [42]. The combination of IL-6 with cardiac troponin T (cTnT) or NT-proBNP can enhance the predictive accuracy for the severity of myocardial injury and prognosis [43]. The neutrophil-to-lymphocyte ratio (NLR) reflects the imbalance between neutrophil-driven inflammation and lymphocyte-mediated immune suppression, and is considered to have good utility in risk stratification and assessing treatment efficacy in CS patients. In CS patients, an NLR > 10 is significantly associated with a 30-day mortality rate, and persistent elevation suggests worsening microcirculatory dysfunction, systemic inflammation, and hemodynamic deterioration [44]. A decrease in NLR after treatment can indirectly reflect myocardial recovery [45]. However, inflammatory biomarkers are influenced by systemic inflammatory conditions such as infections, tumors, and trauma, and their diagnostic accuracy when used alone is not significant. The combined use of specific biomarkers such as cTn and BNP can improve diagnostic accuracy.

Emerging Biomarkers

Emerging Markers of Myocardial Injury

Under conditions of cellular injury or stress (such as myocardial ischemia or low perfusion), high mobility group box 1 (HMGB1) can be actively secreted or passively released into the extracellular space, exacerbating the systemic inflammatory response [46]. In patients with CS, plasma levels of HMGB1 are significantly elevated and are associated with acute kidney injury, liver dysfunction, and neurological complications. HMGB1 is an independent predictor of 30-day all-cause mortality [47]. Animal studies have shown that HMGB1 inhibitors can reduce inflammation and myocardial injury, but clinical research has not yet confirmed their role in improving survival rates [48]. Further multicenter randomized controlled trials are needed to validate the prognostic value of HMGB1 in CS patients and to explore its potential in inhibiting inflammation and improving CS prognosis.

Myocardial light chain (MLC) is a core component of the myocardial myofibrillar contractile proteins. During CS, ischemia-reperfusion injury leads to a decrease in MLC phosphorylation levels and a reduction in contractile force. Plasma levels of MLC are negatively correlated with infarct size and left ventricular ejection fraction, suggesting that MLC may serve as a potential biomarker for assessing the extent of myocardial injury in CS [49]. Animal studies have demonstrated the diagnostic accuracy and development potential of MLC for CS, but clinical trial data are lacking [50]. The application of MLC in the diagnosis and treatment of CS remains challenging, as phosphorylation detection relies on myocardial biopsy, which makes real-time dynamic monitoring difficult. Future efforts should focus on systematic exploration from mechanistic research to clinical translation in order to overcome the treatment bottlenecks of CS [51].

Emerging Cardiac Function Markers

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor-β superfamily, and its expression is low in the myocardium under normal physiological conditions. Under conditions of myocardial ischemia, oxidative stress, or inflammatory stimuli, GDF-15 is significantly upregulated in cardiomyocytes and macrophages via the p53 and NF-κB pathways, with plasma levels potentially increasing to 10–100 times the baseline value [52]. GDF-15 is significantly ele-

vated in patients with AMI and can be used for the early identification of non-ST-segment elevation myocardial infarction [53]. In patients with CS, GDF-15 levels are markedly increased, and its baseline levels are independently associated with 30-day all-cause mortality, with a risk ratio significantly higher than traditional markers such as lactate [54]. In cases of multiple organ dysfunction (e.g., acute kidney injury, microcirculatory disturbances), GDF-15 is significantly elevated and shows a marked decrease after mechanical circulatory support (e.g., ECMO or left ventricular assist device), making it useful for assessing organ damage in CS [55]. Additionally, GDF-15 can inhibit platelet function and has predictive value for bleeding risk in patients undergoing anticoagulant therapy, though clinical data remain limited [56]. GDF-15 has functions in inflammation regulation, cardioprotection, and metabolic modulation, making it suitable for multidimensional risk assessment. However, critical values vary significantly across studies, and further investigation is needed to explore its applicability in both ischemic and non-ischemic CS.

Adrenomedullin (ADM) is secreted by endothelial cells, smooth muscle cells, and cardiomyocytes, and exerts vasodilation, anti-inflammatory, and anti-apoptotic effects through the activation of G protein-coupled receptors [57]. In a multicenter cohort study, the baseline ADM levels were significantly elevated in patients with CS, and were independently associated with the 30-day rehospitalization rate [58]. Notably, the application of ADM still faces challenges. Changes in ADM levels do not influence the 30-day cardiovascular organ support requirements or improve survival rates. Furthermore, the bidirectional effects of ADM (vasodilation and inhibition of platelet activation) may limit the therapeutic benefits, necessitating further exploration of precision intervention strategies [58]. We summarized some common biomarkers (Table 1).

Other Biomarkers

Some studies have also reported biomarkers of CS with distinct functional characteristics: ① Endothelial function and microcirculatory disturbances: Angiopoietin-2 and soluble urokinase plasminogen activator receptor; ② Myocardial suppression and myocardial injury: Circulating dipeptidyl peptidase and apelin; ③ Inflammation/fibrosis and thrombosis: Galectin-3 and fibroblast growth factor-23; ④ Renal injury: Cystatin C, plasma neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1; ⑤ Neurohormonal activation and metabolic disorders: Proenkephalin. The diagnostic specificity of these biomarkers is not high, but their combined use can enhance the effectiveness of CS risk prediction. The characteristics of some emerging biomarkers are shown in Table 2.

Table 1 | Advantages and disadvantages of common CS biological indicators

Biomakers	Concentration change time	Advantages
HMGB1	Shock increased within 24 hours, peaked at 72 hours, and decreased at 96 hours	It reflects inflammation and cell damage, and is related to multiple organ dysfunction
GDF-15	Significantly increased within 24 hours after onset	It reflects multiple organ injuries (such as kidney and liver), and is related to the risk of bleeding, with a short half-life (3 hours)
sST2	It rises rapidly after onset and lasts for 3-4 days	Independent of BMI and renal function, reflecting myocardial fibrosis and inflammatory response
ADM	Significantly increased in refractory shock	It reflects vasodilation and endothelial dysfunction, and is positively correlated with the severity of shock
STREM-1	It was elevated at baseline and maintained high expression at 48-96 hours	Early prediction of organ injury (kidney, liver, endothelium) and mortality, reflecting the activation of systemic inflammation
SAA	It increased 3-6 hours after infection/ inflammation and decreased rapidly during recovery	Rapid reflection of inflammatory state, short half-life (50 minutes), suitable for dynamic monitoring
cTn	It rises at 3-6 hours after myocardial infarction and reaches the peak at 24 hours, lasting for 7-10 days	The "gold standard" for myocardial injury has high sensitivity and can guide revascularization
BNP	It rises several hours after heart failure and has a short half-life (20 minutes)	Real time reflection of ventricular pressure load to guide the treatment and adjustment of acute heart failure
NT-proBNP	It rises several hours after heart failure and has a long half-life (90 minutes)	High in vitro stability, suitable for long-term monitoring, high negative predictive value (excluding heart failure)

Table 2 l The characteristics of some emerging biomarkers

Biomakers	Characteristics
Ang-2	It is negatively correlated with left ventricular ejection fraction, which can independently predict the 30 day and 1-year all-cause mortality in patients with cardiogenic shock, and has nothing to do with the use of IABP
Co-peptin	The improved shock score (such as salmon score) combined with HS cTnT or NT proBNP can improve the accuracy of early diagnosis of cardiogenic shock
cDPP3	The elevated level reflects the stress or necrosis of myocardial cells, and is positively correlated with the deterioration of left ventricular function. It is an independent predictor of 30 day and 1-year all-cause mortality in patients with cardiogenic shock
Gal-3	High baseline Gal-3 levels may indicate the need for early activation of VA-ECMO or left ventricular assist devices
ADM and suPAR	The prediction efficiency is better than BNP and lactic acid, but it will also increase in septic shock, acute respiratory distress syndrome (ARDS) and other critical diseases
Cystatin C and P-NGAL and KIM-1	It is an independent predictor of short-term mortality. The deterioration of renal function in patients with cardiogenic shock was detected 6-12 hours before the increase of creatinine
FGF-23 and P-PENK	Activation of pro-inflammatory pathways (such as NF - κ b) aggravates systemic inflammatory response, which may be related to the progression of multiple organ dysfunction in patients with cardiogenic shock

Summary and Prospect

Over years of development and application, researchers have identified and promoted numerous biomarkers related to CS, some of which have been shown to have very high diagnostic accuracy. It is important to note that CS biomarkers still need to meet the criteria of low cost and high accuracy to facilitate their widespread adoption in medical centers at all levels. The greatest value of CS biomarkers should lie in their integration throughout the entire clinical diagnostic and treatment process. What sets them apart is their ability not only to map out a comprehensive pathological mechanism but also to identify personalized therapeutic targets at the molecular level, enabling precision treatment decisions. It is essential to conduct multi-center, large-sample clinical cohort studies for application validation, and establish a "basic research - clinical application - diagnostic and therapeutic use" translational loop to promote a profound shift in the diagnostic and treatment process from experiential medicine to evidence-based decision-making.

Funding The present article was supported by the National Key Clinical Specialty Construction Project, Guangxi Medical And Health Key Discipline Construction Project, Guangxi Key Clinical Specialty Construction Project.

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