

Diagnostic and prognostic value of biomarkers in acute myocardial infarction

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ABSTRACT

The incidence of acute myocardial infarction (AMI) has been increasing rapidly in recent years, seriously endangering human health. Cardiac biomarkers play critical roles in the diagnosis and prognosis of AMI. Troponin is a highly sensitive and specific biomarker for AMI diagnosis and can independently predict adverse cardiac events. Other biomarkers such as N-terminal B-type natriuretic peptide and C reactive protein are also valuable predictors of cardiovascular prognosis. Recently, several novel biomarkers have been identified for the diagnosis and risk assessment in patients with AMI. A multibiomarker approach can potentially enhance the diagnostic accuracy and provide more information for the early risk stratification of AMI. In this review, we will summarise the biomarkers discovered in recent years and focus on their diagnostic and prognostic value for patients with AMI.

INTRODUCTION

Biomarkers of cardiac injury have been used to diagnose acute myocardial infarction (AMI) for over half a century. Karmen *et al*¹ first reported the elevation of aspartate transaminase (AST) in patients with AMI in 1954. AST was the first cardiac biomarker used in clinical practice. However, it became clear that AST had limited use as a cardiac biomarker due to the lack of specificity for myocardial injury.^{2,3}

In the following years, creatine kinase (CK) was defined as a more sensitive and specific biomarker and lactate dehydrogenase (LDH) was also discovered. However, specificity continued to be problematic, especially for patients with muscle and liver disease or injury. Later development of new detection methods identified CK-MB as a molecule showing higher diagnostic accuracy. Unfortunately, CK, LDH and CK-MB still lacked specificity for diagnosing AMI.^{4,5}

Rapid advances in laboratory techniques and the clinically urgent need resulted in the discovery of cardiac troponins (cTns).⁶ The guidelines have recommended cTn as the preferred biomarker due to its sensitivity and cardiac specificity.⁷ In this review, we summarise the biomarkers discovered in recent years and focus on their diagnostic and prognostic value in AMI.

SUMMARY OF CARDIAC BIOMARKERS

Myocardial necrosis biomarkers

Cardiac troponins (cTns)

Troponins are important for actin and myosin interaction, and regulation of cytoplasmic contractile function in response to cytosolic calcium and

protein phosphorylation. The troponin complex is located along with tropomyosin on the actin filament. Cardiac-specific isoforms of cTnI and cTnT exist in myocardial tissue, whereas troponin C is also expressed in skeletal muscle, rendering it unsuitable for the purposes of AMI diagnostic.⁸

The Third Universal Definition of Myocardial Infarction requires detection of a significant elevation and decline in serum cTn level with at least one value above the 99th percentile of the upper reference limit; moreover, cTn levels should be measured with a coefficient of variation of $\leq 10\%$.⁹ The development of high-sensitivity troponin (hs-cTn) analysis improved the identification of myocardial injury, with abnormal cTn detected within 24 hours.^{10–13}

Although elevated serum cTn levels reflect myocardial damage, the mechanistic basis for this observation remains unclear. In addition to spontaneous AMI following acute coronary occlusion and plaque rupture, AMI can be secondary to ischaemia resulting from increased demand for or decreased supply of oxygen, coronary embolism, coronary artery spasm, arrhythmia and hypertension. Consequently, cTn levels may be upregulated in coronary disease and also in non-cardiac disorder.^{14,15} Indeed, cTn level is increased in patients with renal failure without symptoms of acute coronary syndrome (ACS), although they are at increased risk of cardiac abnormalities. Another study reported that 50% of patients with renal failure and high cTn level had coronary arteries free of flow-limiting stenosis in an angiography,¹⁶ implying that cTn is chronically elevated in these individuals.

High cTn level is useful for diagnostic purpose and is also an independent prognostic marker, as evidenced in several clinical trials and a meta-analysis.^{17,18} cTn level can inform clinical decision-making in terms of whether a more aggressive or conservative treatment course should be adopted after ACS since abnormalities can identify subgroups of patients greater benefit from early invasive therapy.¹⁹

Myoglobin

Myoglobin is a low molecular weight cytoplasmic heme protein that is the most sensitive conventionally assayed biomarker of AMI. Nevertheless, myoglobin has lower specificity for cardiac necrosis than cTnI and its expression may be upregulated in non-cardiac disorders, such as skeletal muscle disease or injury and chronic renal disease.^{20,21} Despite lack of cardiac specificity, combining myoglobin with troponin significantly improved the ability to identify those at risk of



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increased mortality from AMI as compared with either marker individually.^{22 23} Myoglobin is primarily eliminated through the kidneys, and renal insufficiency is recognised as a predictor of adverse outcome, including mortality, in patients with AMI.²⁴ Thus, it is presumed that myoglobin predicts mortality by identifying patients with renal insufficiency.

Ischaemia-modified albumin

In acute ischaemia, the N terminus of albumin is altered, thereby reducing its binding capacity, and the resultant protein is referred to as ischaemia-modified albumin (IMA). In patients with suspected ACS, the diagnostic accuracy at presentation increased when IMA was used in conjunction with cTnT and ECG findings.²⁵ In fact, IMA in combination with initial cTnT is more sensitive than the latter alone for predicting adverse cardiac events, although the specificity and sensitivity for IMA are too low to be useful for clinical decision-making.²⁶

Heart-type fatty acid binding protein (hFABP)

hFABP is a small cytoplasmic protein present in cardiomyocytes that is similar to myoglobin. It is rapidly released into the circulation after the onset of myocardial injury owing to its low molecular weight and cytoplasmic localisation.²⁷ Agnello *et al*²⁸ found that early diagnosis of AMI was possibly based on measurement of hFABP level. However, hFABP expression is not cardiac specific, being detected at low levels in skeletal muscle and kidney.²⁹ The diagnostic value of hFABP remains controversial. The prognostic value of hFABP in patients with suspected ACS has been investigated in several studies. High hFABP level was the best predictor of adverse events during a 1-year follow-up in patients with non-ST-elevation MI (NSTEMI) among markers of myocardial necrosis (hFABP, cTnI and CK-MB).³⁰ Serial measurements of hFABP at the time of admission and discharge provided information about cardiac events in patients with chronic heart failure, and those with persistent elevation of hFABP had the highest rate of cardiac events, including cardiac deaths and rehospitalisations.³¹ However, hFABP has not been accepted as a standard biomarker of ACS, owing to certain technical issues that are discussed elsewhere.³²

Neuroendocrine biomarkers

BNP/NT-proBNP

B-Type natriuretic peptide (BNP) is a hormone secreted by cardiomyocytes in the heart ventricles in response to cardiac stress and ventricular dysfunction. After its synthesis the proBNP precursor is cleaved into the active BNP hormone and an inactive NT-proBNP fragment. The functions of BNP include vasodilatation, natriuresis and inhibition of the renin–angiotensin–aldosterone system.³³

Serum levels of cardiac natriuretic peptides, especially BNP and NT-proBNP, are upregulated following ACS.³⁴ Elevated BNP levels in patients with AMI were also found to be associated with myocardial infarct size.³⁵ Although BNP/NT-proBNP levels are increased in patients with ACS, they cannot be used as diagnostic markers since they are also upregulated in other conditions with similar symptoms such as heart failure and pulmonary embolus. Due to partial clearance of BNP and NT-proBNP by renal excretion, patients with renal insufficiency also have high levels of BNP and NT-proBNP.³⁶

Several studies have demonstrated the prognostic value of BNP and NT-proBNP in patients with myocardial infarction. Plasma NT-proBNP, measured 2 to 4 days after AMI, independently predicted left ventricular function and 1-year

survival.³⁷ Increased BNP level at initial presentation of patients with STEMI was associated with impaired reperfusion after fibrinolysis and higher 30-day mortality. After adjusting for cTnI, BNP remained independently associated with mortality and the rates of heart failure and death increased with higher baseline concentrations of BNP.³⁸

It was reported that BNP and NT-proBNP were better at predicting cardiovascular events than Thrombolysis In Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) risk score. The predictive value of NT-proBNP was independent and the combination of NT-proBNP and TIMI or GRACE score did not significantly improve prediction of short-term mortality risk.^{39 40}

Both BNP and NT-proBNP are excellent biomarkers of adverse events post-AMI; however, there is no consensus on whether they can be used to guide early treatment in order to improve patients' outcomes because of their demonstrated role in the diagnosis and management of heart failure.

Adrenomedullin

Adrenomedullin is a cardiovascular regulatory peptide whose levels are increased in the serum of patients with cardiovascular disease. It attenuates infarct development during acute myocardial injury and can potentially influence the pathological process in both the acute phase of AMI and subsequent remodelling. Elevated adrenomedullin levels are indicative of cardiac remodelling and may improve risk stratification in heart failure and MI.^{41 42}

Renin–angiotensin–aldosterone system (RAAS)

The RAAS is a hormone system that regulates blood pressure and fluid balance. It is activated following AMI, by the increased volume blood and vasoconstriction. Aldosterone promotes a broad range of detrimental cardiovascular effects during AMI, including acute endothelial dysfunction, increased endothelial oxidative stress, cardiac myocyte necrosis, and myocardial hypertrophy and fibrosis.

With the exception of BNP, the aforementioned neuroendocrine markers are not yet routinely used in clinical practice for diagnosis or prognosis. However, studies have shown that treatment of patients with AMI with inhibitors of the neuroendocrine system reduced morbidity and mortality, for instance, rates of death and heart failure in patients with ACS decreased by administration of ACE inhibitor/angiotensin receptor blocker and aldosterone inhibitors.^{43 44}

Inflammatory biomarkers

C reactive protein (CRP)

Inflammation plays an important role in the pathogenesis of atherothrombosis and ACS. CRP is an acute-phase inflammatory response biomarker, produced by hepatocytes on stimulation by inflammatory cytokines, primarily interleukin-6 (IL-6), that associated with increased cardiovascular risk in patients with established atherosclerosis. Several studies have reported that upregulation of CRP is an independent prognostic marker of recurrent non-fatal MI or cardiac death.^{45 46} It also reflects the extent of myocardial injury in STEMIs. Wang *et al*⁴⁷ found that serum CRP was increased in patients with AMI suggesting that circulating CRP is a potential diagnostic biomarker. Despite some positive results, CRP is not considered to have sufficient specificity and sensitivity for use as a reliable diagnostic marker.^{48 49}

Nonetheless, CRP is a significant predictor of poor outcome. Lukin *et al*⁴⁶ found that plasma CRP level predicted major

Table 1 Summary of biomarkers in acute myocardial infarction

Biomarkers	Diagnostic value	Prognostic value	
Myocardial necrosis	AST ¹⁻³	First biomarker of AMI but lacks specificity	No data
	CK/CK-MB ⁴	Not as sensitive or specific as cTn	Not consistently predictive of adverse events
	Troponin ⁵⁻¹⁹	Highly sensitive and specific, current 'gold standard' for AMI diagnosis	Independent predictor of adverse events
	Myoglobin ²⁰⁻²⁴	Sensitive early after symptom onset, negative predictive value, but lacks specificity	Predictive of mortality in renal insufficiency
	IMA ²⁵⁻²⁶	Less sensitive than cTn and lacks specificity	Possibly predictive of adverse events
	hFABP ²⁷⁻³²	Sensitive early after symptom onset, but lacks specificity	Predictive of mortality
Neuroendocrine	BNP/NT-proBNP ³³⁻⁴⁰	Not sensitive or specific	Highly predictive of heart failure and mortality
	Adrenomedullin ⁴¹⁻⁴²		Possibly predictive of adverse events
	RASS ⁴³		
Inflammation	CRP ⁴⁷⁻⁵⁴	Not sensitive or specific. The diagnostic accuracy of cTn can be increased when combining with some of these inflammatory biomarkers	Possibly predictive of heart failure and mortality
	IL-6 ⁵⁵⁻⁵⁷		
	TNF- α ⁵⁸		
	PCT ⁵⁹⁻⁶¹		
	MPO ⁶²⁻⁶⁴		
	MMP ⁶⁵⁻⁶⁶		
	sCD40L ⁶⁷		
	PGF ⁶⁸		
Other novel cardiac biomarkers	miRNAs ⁶⁹⁻⁷⁸	Raised but not sensitive or specific for AMI	Possibly predictive of mortality and heart failure
	ST2 ⁷⁹⁻⁸¹	Raised but not sensitive or specific for AMI	Predictive of mortality and heart failure
	GDF-15 ⁸²⁻⁸⁴	Raised but not sensitive or specific for AMI	Predictive of mortality and ischaemia
	Gal-3 ⁸⁵⁻⁸⁹	Raised in AMI but insufficient data	Possibly predictive of adverse events

AMI, acute myocardial infarction; cTn, cardiac troponin; IMA, ischaemia-modified albumin.

adverse cardiac events in patients with ACS, and other studies confirmed that a higher CRP level is associated with increased long-term risk of recurrent cardiovascular events or death.⁵⁰ Serum concentration of high-sensitivity CRP (hs-CRP) is a sensitive indicator of inflammation which is closely related to plaque formation and is an independent prognostic marker in patients with ACS^{51,52}; it has therefore been recommended as a guide for treatment decisions. However, several studies showed that CRP is unrelated to the occurrence of AMI, and that only cTn, not CRP, is useful for identifying patients who will benefit from an invasive strategy or antithrombotic treatment.^{53,54}

Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)

IL-6 and TNF- α are two major pro-inflammatory markers. The former is involved in inflammatory cell activation and recruitment, and stimulates the liver to produce acute-phase proteins such as CRP while exerting a negative inotropic effect through myocardial nitric oxide synthase (NOS). Wang *et al*⁵⁵ found that IL-6 was related to the procession of ACS and had prognostic use. Serum IL-6 was shown to be useful for predicting mortality in patients with ACS⁵¹ and identifying individuals who could benefit from targeted interventional or intensive therapy.⁵⁶ However, the circadian fluctuation in IL-6 levels and a lack of confirmatory studies have limited the use of IL-6 as an effective biomarker of ACS.⁵⁷ TNF- α is a cardio-inhibitory cytokine, detected in several tissues including endothelial cells, smooth muscle cells and macrophages that reduces cardiac contractility either directly or via induction of NOS. It was reported that inflammatory cytokines, including TNF- α and hs-CRP, could predict the 6-month survival of patients with ACS.⁵⁸

Procalcitonin

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, which is involved in calcium homeostasis. It has also been

shown to be induced under inflammatory conditions. Kafkas *et al*⁵⁹ showed that the PCT concentration was increased in patients with AMI. Other studies also have found that PCT have prognostic value for predicting mortality or other ischaemic events.^{60,61***}

Markers of plaque destabilisation

Myeloperoxidase (MPO) is a component of granules within the neutrophils. It plays a crucial role in inflammation and oxidative stress in the cellular level.⁶² Studies have shown that MPO is inferior to current biomarkers for diagnostic purposes, but elevated levels independently predict future risk of coronary artery disease in both patients with ACS and healthy individuals.⁶³ Among patients with ACS, baseline MPO has been shown to be an independent predictor of adverse cardiac events. Omran *et al*⁶⁴ also found that the use of baseline levels of three biomarkers in combination (MPO, CK-MB and cTnI) could increase early diagnosis accuracy of AMI.

Matrix metalloproteinases (MMPs) are a family of zinc-containing endoproteases, which plays an important role in the physiology and pathology of the cardiovascular system.⁶⁵ MMPs, in particular MMP-9, are important in the collagen breakdown and structural changes associated with ventricular remodelling after AMI and a distal biomarker for inflammation.⁶⁶

Markers of myocyte rupture

The CD40 and CD40 ligand (CD40L) system is expressed on a variety of cell types. Studies suggest that elevated serum levels of soluble CD40L (sCD40L) identify patients with ACS at higher risk of recurrent MI and death independent of other prognostic biomarkers including cTnI and CRP,⁶⁷ and the subgroup of patients who will benefit from antiplatelet treatment can be identified.

Placental growth factor (PGF) is associated with angiogenesis and vasculogenesis, which has been implicated in neovascularisation in ischaemic myocardium and promoting atherosclerosis. Higher concentration of PGF after ACS is associated with long-term risk of recurrent cardiovascular events independent of traditional risk factors.⁶⁸

Other novel cardiac biomarkers

MicroRNAs (miRNAs)

In recent years, several cardiac-specific miRNAs have been identified to play important roles in the development of cardiovascular diseases.⁶⁹ Among these miRNAs, four cardiac-enriched miRNAs (miR-208, miR-499, miR-1 and miR-133) are consistently found to be increased in the plasma of patients with AMI.⁷⁰ Devaux *et al*⁷¹ indicated that concentrations of miR-208b, miR-499 and miR-320a were significantly elevated in patients with AMI. Recently, miR-92a and miR-181a were used as potential biomarkers for the diagnosis of AMI.^{72 73} Oerlemans *et al*⁷⁴ revealed that the combination of miR-1, miR-21 and miR-499 had a higher diagnostic value than hs-troponin T. In addition to diagnostic value, miRNAs may be more useful for risk stratification and can be used as prognostic biomarkers.⁷⁵ Circulating miRNA-197 and miRNA-223 were identified as predictors for cardiovascular death in a large patient cohort with coronary artery disease.⁷⁶ Studies also found that miRNA-134, miRNA-328, miRNA-34a and miRNA-208b were associated with the development of heart failure and increased risk of mortality after AMI.^{77 78}

Suppression of tumourigenicity 2 (ST2)

ST2 is a biomarker of cardiomyocyte stress and fibrosis, which has been shown to be induced in conditions of MI and acute heart failure which causes myocardial overload.⁷⁹ Studies have reported elevated level of ST2 in patients with ACS but would not be a reliable diagnostic marker because of the lack of specificity. These studies also suggested that ST2 has the ability to predict mortality and heart failure in patients with ACS.^{80 81}

Growth differentiation factor-15 (GDF-15)

GDFs are a protein subfamily belonging to the transforming growth factor beta superfamily. GDF-15 increases during tissue injury and inflammatory states and is associated with cardiometabolic risk.⁸² Studies have suggested that circulating concentration of GDF-15 is elevated in patients with AMI⁸³ and can independently predict mortality or a composite of death and non-fatal AMI. Other studies also found that risk stratification can be improved by measuring both cTnT/NT-proBNP and GDF-15 levels.⁸⁴

Galectin-3 (Gal-3)

Gal-3 is involved in cardiac fibrosis, inflammation and reconstruction processes. Several studies have showed that circulating Gal-3 levels are elevated in AMI.^{85 86} In addition, Gal-3 is associated with ventricular remodelling and elevated plasma Gal-3 levels are related to lower left ventricular ejection fraction.⁸⁷ Moreover, Gal-3 is also suggested as a valuable predictive marker in patients with coronary artery disease and ischaemic stroke.^{88 89}

MULTIBIOMARKER APPROACH

Ideal biomarkers should show high sensitivity, especially in the first few hours after symptom onset.⁹⁰ A single cTn test may not provide sufficient sensitivity for early diagnosis of

AMI owing to its delayed release, even in the case of hs-cTn. Distinct pathways in the complex pathophysiology of AMI have been revealed by the identification of novel cardiac biomarkers. Several studies have suggested that adding tests for different biomarkers to cTn detection can improve diagnosis as well as prediction of short-term and long-term prognosis. Furthermore, the rational basis for cardiovascular risk assessment can be enhanced by employing a multibiomarker strategy that relates to various aspects of ACS.

Baseline levels of cTnI, CRP and BNP are independent predictors of adverse events following AMI. Kim *et al*⁹¹ confirmed that a combination of hs-CRP and NT-proBNP had greater value in predicting short-term cardiac events in patients with ACS than either marker alone. It was also demonstrated that combining biomarkers across the axes of myocardial stress, inflammation and myocyte necrosis improved prediction of cardiovascular death or heart failure.⁹² Additionally, low-risk patients identified based on negativity for cTnI/CK-MB/myoglobin had a low mortality.⁹³ Other marker combinations include hFABP/cTn, which improved early diagnostic use⁹⁴ compared with cTn only and hFABP/NT-proBNP/cTnI,⁹⁵ IL-10/MPO/PGF/cTnI⁹⁶ and

Main messages

- ▶ The incidence of acute myocardial infarction (AMI) has been increasing rapidly in recent years.
- ▶ Cardiac biomarkers play critical roles in the diagnosis and prognosis of AMI.
- ▶ The multi-biomarker approach can increase the diagnostic accuracy and provide more information for the risk stratification of AMI.

Current research questions

- ▶ Are there other novel biomarkers for the diagnosis of AMI in addition to troponin?
- ▶ Which biomarkers can be used to evaluate the prognosis of patients with AMI?

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Self-assessment questions

- Acute myocardial infarction is diagnosed based on the following evidence:
 - Typical chest pain lasts more than half an hour
 - Dynamic evolution of ECG
 - Cardiac dysfunction detected by echocardiography
 - Increased serum levels of troponin
- Which biomarkers are sensitive at the early stage of acute myocardial infarction?
 - Myoglobin
 - AST
 - CKMB
 - Troponin
- Which of the following biomarkers has the optimal sensitivity and specificity for diagnosing acute myocardial infarction?
 - Myoglobin
 - AST
 - CKMB
 - Troponin
- Which biomarkers can be used to evaluate the prognosis of patients with myocardial infarction?
 - Troponins
 - hFABP
 - NT-proBNP
 - CRP
- Which of the following descriptions is correct?
 - We should search for novel biomarkers
 - Serum biomarkers are golden standard for diagnosing diseases
 - We should develop multibiomarker approach
 - Current biomarkers are sufficient enough

ST2/GDF-15/hFABP/hs-TnT,⁹⁷ which have been proposed as prognostic aids but need further prospective research.

On the other hand, various arguments have been made against the multibiomarker approach. Feistritz et al⁹⁸ found that the predictive value of hs-cTnT was not further improved when combined with CK, hs-CRP, LDH, AST and ALT. Others have demonstrated that once a single strong predictor of risk (eg, cTn) is included in a combination of markers, it is difficult to quantify the contribution of the latter to predictive models. The relative risk relationships for individual biomarkers and specific end points differ, which can introduce variability in the risk assessment and influence therapeutic decision-making.

SUMMARY

In this review, we summarise the biomarkers discovered in recent years and focus on their diagnostic and prognostic value in patients with AMI (table 1). The ideal biomarkers of AMI should be sensitive and specific in the early period after the onset of symptoms and provide prognostic information for risk assessment, which could guide clinicians to identify the best treatment options. cTn is a highly sensitive and specific cardiac biomarker for AMI diagnosis and can independently predict adverse cardiac events, including death and heart failure. Other biomarkers such as BNP/NT-proBNP and CRP are also valuable predictors of cardiovascular prognosis. In recent years, several novel biomarkers have been identified for the diagnosis and risk assessment in patients with AMI. A multibiomarker approach can potentially enhance the diagnostic and prognostic accuracy and may have broad clinical application prospects.

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Answers

1. A-True; B-True; C-False; D-True
2. A-True; B-True; C-True; D-True
3. A-False; B-False; C-False; D-True
4. A-True; B-True; C-True; D-True
5. A-True; B-False; C- True; D-False