REVIEW

Biomarkers in the prediction and management of acute coronary syndromes: current perspectives

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Abstract: A large branch of research has focused on the search for biomarkers for early detection of myocardial cell injuries. Most of these studies have evaluated patients presenting to the emergency department, underlining the need for an ideal biomarker for rapid recognition of acute coronary syndrome (ACS). In the recent past, diagnosis of ACS in the emergency department has been based mostly on clinical information and electrocardiographic findings, and markers of generic cell damage have been used to support clinical suspicion. Over the last few years, the role of markers has taken up increasingly more space in non-life-threatening conditions, confining the clinical examination of the patient to the mere waiting for results of blood tests after the electrocardiograph. Currently, the biomarkers most widely used for the diagnosis of ACS are cardiac troponins. Since their introduction into clinical practice, several generations of commercial cardiac troponin assays have been validated in analytical and clinical trials. Development of newer high-sensitivity assays seems to have improved the value of cardiac troponin as both a diagnostic and risk indicator. Several other biomarkers of ACS apart from cardiac troponin have been investigated, but most still require validation in further studies. Among these, pregnancy-associated plasma protein-A, ischemia-modified albumin, and heart-type fatty acid binding protein seem to be the most promising markers under investigation for their possible usefulness in the emergency department setting for early diagnosis of ACS. In conclusion, a multimarker approach could be the future of research. In this review, we highlight the old and new markers, especially the most studied and widely used in clinical practice in recent years, particularly those that can help the clinician to make a rapid and confident diagnosis of ACS.

Keywords: biomarkers, acute coronary syndrome, myocardial infarction, emergency department

Introduction

Biomarkers are biological molecules found in blood and are used as markers of physiologic or pathologic processes taking place in the body. The National Institutes of Health define a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological process and pathogenic process".[1] In recent years, a large body of research has focused on the search for biomarkers for early detection of myocardial cell injuries. Most of these studies have evaluated patients presenting to emergency departments, underlining the need for an ideal biomarker for rapid recognition of acute coronary syndrome (ACS).

ACS is an extensive term accounting for any condition causing sudden reduced blood flow to the heart, the common feature of which is chest pain. ACS includes three main clinical presentations, ie, ST-elevation myocardial infarction (MI), non-ST-elevation

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MI, and unstable angina. Despite the lack of a universally accepted definition of unstable angina, it has been described as a clinical syndrome between stable angina and acute MI.[2] Unstable angina and non-ST-elevation MI are considered closely related conditions, with clinical presentations that may be indistinguishable. The term "myocardial infarction", according to Thygesen et al,[3] should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. This evidence is mostly given by detection of high levels of a sensitive and specific biomarker in the bloodstream.

In the recent past, diagnosis of ACS in the emergency department was based mainly on clinical information and electrocardiographic (ECG) findings, and markers of generic cell damage were used to support clinical suspicion. Over the last few years, the role of markers has taken up increasingly more space in non-life-threatening conditions, confining the clinic in that narrow space between the execution of the ECG and the waiting of the biomarkers assay report.

In this review, we highlight the old and new markers, especially the most studied and widely used in clinical practice in recent years and particularly those that can help the clinician to make a rapid and confident diagnosis of ACS (Table 1).

Methods

We performed a literature search using PubMed/MEDLINE (1968–2013) to identify and evaluate all relevant English-language studies of cardiac biomarkers in the prediction of ACS. The search strategy was conducted following previously published principles.[4,5] We used the following key words "myocardial infarction", "cardiac biomarker", "acute coronary syndrome", and "troponin". Articles were also identified by a manual search of bibliographies from retrieved articles. The literature search was conducted by two reviewers independently of one another, and any discrepancy was resolved by consensus with a third author. We used the GRADE system to evaluate the overall quality of the evidence and the strength of the recommendations.[6]

Cardiac troponins

The biomarkers most widely used for the diagnosis of ACS are the cardiac troponins.[7] The troponin complex is an intra-cytoplasmic protein constituted by three subunits (C, I, and T) which together control calcium-mediated interaction between actin and myosin, resulting in the contraction and relaxation of striated muscle. Specifically, troponin C binds to calcium ions to produce a conformational change in troponin I, troponin T binds to tropomyosin, and troponin I binds to actin to hold the troponin-tropomyosin complex in place.[8] The troponin T and I subunits are expressed only in cardiac muscle, which allows these biomarkers to be highly specific for myocardial damage. After myocardial cell death, cardiac troponin levels remain detectable for days (4–7 days for subunit I and more than 10–14 days for subunit T). However, detection of troponin in the blood could be delayed in myocardial injury, given that cellular necrosis typically requires 2–4 hours to take place after an ischemic event. For this reason, serial measurements are recommended to be taken at presentation and 6 hours after the onset of symptoms.[9]

Since their introduction into clinical practice, several generations of commercial cardiac troponin T and I assays have been validated in analytical and clinical trials. Development of the newer high-sensitivity cardiac troponin T assays seems to have improved the value of cardiac troponin as both a diagnostic and risk indicator. Furthermore, there are some data suggesting that a negative troponin result reflects a good prognosis due to the low incidence of cardiac death or non-fatal MI at 30 days.[10]

The current recommendations of medical societies are for a single decision limit for MI diagnosis and risk stratification at the 99th percentile of a reference population for each assay. New generations of sensitive assays for cardiac troponin with a 10% coefficient of variation for levels below the 99th percentile have been introduced in recent years.[11] This approach may identify more patients at risk and lead to earlier diagnosis. In patients with known coronary disease, cardiac troponin T levels above the 99th percentile were associated with an increased risk of future cardiovascular events.[12,13] Furthermore, the high-sensitivity assays measure quantifiable circulating levels of cardiac troponin T below the 99th percentile in patients with mild coronary artery disease.[14,15] Finally, the high-sensitivity assays allow detection of circulating cardiac troponin in healthy individuals, and therefore definition of a normal range.[16,17] However, recent research shows reduced performance of troponin T in elderly patients,[18] and this could indicate a need for further studies to investigate a different cutoff based on age and presence of comorbidities.

In addition to acute myocardial infarction secondary to plaque rupture and coronary occlusion, troponin release into the bloodstream can be secondary to ischemia produced either by increased oxygen demand or decreased supply. Thus, troponin elevation may occur in patients with severe anemia, arrhythmias, hypertension or hypotension, pulmonary embolism, coronary artery spasm, or coronary embolism.[19,20] Cardiac troponin is also elevated in patients with renal failure,

myocarditis, pericarditis, congestive cardiac failure, left ventricular hypertrophy, and diabetes without the symptoms of ACS, but in these cases cardiac troponin is not always related to an ongoing acute MI.[21]

From 2010 onwards, technologic advances allowed widespread availability of a new generation of sensitive cardiac troponin assays for early detection of very small troponin concentrations.[22] The new high-sensitivity troponin assays are able to measure troponin concentrations that are lower by a factor of ten than those measurable with conventional assays. Januzzi et al[23] tested the diagnostic performance of troponin T and high-sensitivity troponin and correlated them with the clinical syndrome and with cardiac abnormalities demonstrated on computed tomography angiography. The area under the curve for diagnosis of ACS was 0.79 for highly-sensitive troponin T and 0.74 for cardiac troponin T (highly-sensitive troponin T detected 27% more cases of ACS). Using the 99th percentile cut point for a healthy population, highly-sensitive troponin T had a sensitivity of 62% and a negative predictive value for ACS of 96% (standard troponin T assay had 35% and 93%, respectively), with a specificity of 89% and a positive predictive value of 38% (standard troponin T assay had 99% and 72%, respectively).

In conclusion, troponin results must be interpreted according to the clinical context in which they are measured. Recent studies suggest that observing the trend of cardiac troponin in serial measurements can increase diagnostic specificity. The National Academy for Clinical Biochemistry has recommended changes in cardiac troponin of ≥20% from elevated baseline values, but makes no recommendation on a threshold change from normal initial levels.[24] If this dynamic change is not present, other diagnoses should be considered. In this context, recent studies have shown that absolute rather than relative changes perform better in this setting.[25]

Myoglobin

Myoglobin is one of the most studied proteins in biology. It is an iron-oxygen binding protein and the primary oxygen-carrying pigment in all muscle tissue. Studied as far back as 1958,[26] its role is to transport oxygen with high affinity within the muscle cells by using the bond between oxygen and the "heme" group that gives muscles their characteristic red color.

Myoglobin is released from damaged muscle tissue, where it is present in very high concentration, and is considered a sensitive marker for muscle injury. For many years, it was used as a marker of MI despite the fact that its specificity is very low, given that it is raised in many other conditions, such as skeletal muscle disease and renal impairment. Myoglobin is a smaller protein than creatine kinase (CK) MB and cardiac troponin is released as early as 1–2 hours after onset of ACS symptoms, with levels returning to normal within 24 hours. For this reason, myoglobin is still used in clinical practice in association with more specific biomarkers because of its rapid increase and normalization, which make it useful in patients with chest pain who present early.[27] Moreover, according to Kontos et al,[28] elevated myoglobin has been shown to be a strong predictor of mortality, even in patients with renal impairment. However, in the context of the newer high-sensitive cardiac troponin assays, routine measurement of myoglobin in the assessment of patients with possible ACS has largely been downgraded.[29]

CK-MB isoenzyme

CK, also called phosphokinase, is an enzyme present in many tissues and is especially represented in muscle cells. Its function is to catalyze the conversion of creatine to phosphocreatine, consuming ATP and releasing energy for muscle contraction. It consists of two subunits indicated by the letter B (from brain) and M (from muscle). While in the brain it is mainly represented by the subunit BB (about 96%) and in skeletal muscle cells by the subunit MM (about 90%), in myocardiocytes the enzyme isoforms consist of 60% CK-MM and 40% CK-MB.

For many years, CK-MB activity or mass dosage was used in the diagnosis of MI because of its early release pattern (2–4 hours after cardiac injury). In particular, from studies carried out by Fesmire et al,[30,31] increments in the value of CK-MB over a period of 2–4 hours demonstrated an important role in ruling out ACS in an emergency department setting.[32] Further studies were then performed in the emergency department analyzing CK-MB by itself and in combination with newer markers, all of these showing the ability of CK-MB variation to rule out patients without ACS.[33,34]

Given the prolonged half-life of cardiac troponin, current guidelines recommend CK-MB mass dosage in combination with other more specific markers (such as cardiac troponin and myoglobin) in the evaluation of patients with suspected reinfarction soon after acute MI or cardiac surgery.[35,36] CK-MB mass dosage is also recommended if cardiac troponin dosage is unavailable.

Adiponectin

Adiponectin is an adipocytokine secreted by adipose tissue. Adiponectin is secreted into the bloodstream by mature adipocytes as three oligomeric complexes, ie, a trimer,

hexamer, and a high molecular weight multimer. It has been shown to accumulate in the vascular subendothelial space after damage to the endothelial barrier, where it inhibits adhesion of monocytes to endothelial cells and modulates endothelium-dependent vasodilatation.[37] Adiponectin acts as an endogenous modulator ameliorating obesity-associated complications and is inversely correlated with cardiovascular risk factors such as type 2 diabetes mellitus, hypertension, dyslipidemia, smoking, and coronary artery disease.[38,39]

Several studies have shown a correlation between low baseline plasma adiponectin and increased risk of acute MI in healthy subjects,[40,41] although this correlation may be not valid for women[42] or older Blacks.[43] However, in patients with cardiovascular disease or type 2 diabetes mellitus and high plasma adiponectin levels, an increased risk of all-cause mortality and cardiovascular events has been demonstrated.[44–46] These studies suggest that there may be a paradoxical increase in adiponectin levels in patients with active vascular or myocardial remodeling (including ACS or heart failure). Recently, a large cohort study[47] showed that low-moderate adiponectin levels were associated with a decreased risk of vascular events despite an elevated vascular risk profile. Therefore, further studies are needed to elucidate the usefulness and potential role of adiponectin as a diagnostic/prognostic cardiac biomarker.

Brain natriuretic peptide

Natriuretic peptides are vasoactive hormones secreted by the heart in response to wall stress and myocyte stretch. After synthesis, the precursor, pro-brain natriuretic peptide (BNP), is cleaved to form the physiologically active hormone BNP and an inactive amino-terminal fragment, NT-proBNP. NT-proBNP has a longer half-life, and both BNP and NT-proBNP may accumulate in patients with renal insufficiency due to reduced renal excretion. BNP determines vasodilatation, natriuresis, and inhibition of the renin-angiotensin-aldosterone system, and is released into the serum during ventricular dysfunction and cardiac ischemia.[48,49] BNP levels reach a peak between 14 and 40 hours after an ischemic event. Some patients have a biphasic release with a secondary peak at 5 days.[50–52] It has been suggested that this pattern reflects the development of left ventricular systolic dysfunction, which is prognostically unfavorable compared with a monophasic response.[53] Many studies have shown that both BNP and NT-proBNP provide a prognostic index in those with ACS.[54–56] However, they are not useful diagnostic markers due to their levels being raised in other diseases, such as heart failure and pulmonary embolism.[57,58]

Cathepsins

Cathepsins are a family of proteases widely expressed in human cells, especially in the lysosomes of cells in the reticulohistiocytic system. Given their involvement in inflammatory processes and their correlation with atherosclerosis, cathepsins have been under investigation from more than a decade,[59] looking for implications in early detection of plaque rupture and cardiovascular events. Shalia et al[60] showed a significant elevation of cathepsin B and K levels in the bloodstream of patients with acute MI, while previous studies detected a significant increase of cathepsin L levels in the serum and saliva of the same type of patients.[61] However, looking at recent studies, cathepsins seems to be more helpful in clinical practice for evaluation of cardiac remodeling after MI[62,63] rather than early diagnosis of ACS in the emergency department.

CD40 ligand

CD40 ligand (CD40L) is a cellular cytokine expressed by activated platelets, stimulated lymphocytes, endothelial cells, smooth muscle cells, and macrophages. It is released into the peripheral circulation as soluble CD40L after being cleaved by proteases.[64,65] CD40L has a potential role as a proinflammatory and procoagulant mediator, so has been investigated as a prognostic biomarker of atherothrombotic risk, especially in patients with acute myocardial infarction.[66] Furthermore, increased CD40L levels have been observed in unstable angina,[67] diabetes,[68] obesity,[69] and hypercholesterolemia.[70] However, there is still poor evidence for its use in clinical practice as a diagnostic biomarker[71,72] and contrasting evidence for its use as a prognostic biomarker.[73–76]

Copeptin

Also known as CT-proAVP, copeptin is the C-terminal portion of arginine-vasopressin precursor (AVP or anti-diuretic hormone). Copeptin is a very stable glycopeptide released together with AVP during common precursor (named pre-pro-vasopressin) processing by the posterior pituitary gland. Unlike AVP, which is unstable with a very short half-life (only 5–15 minutes), copeptin can be confidently measured in the serum.

Copeptin levels were shown to be higher in patients with MI, and as a result of its early release into the blood,[77] copeptin showed higher sensitivity than myoglobin.[78] It has been demonstrated that copeptin improves the accuracy of NT-proBNP[79] and the standard cardiac troponin dosage in the first hour after presentation in the emergency department.[80–82] However, the development of new high-sensitivity cardiac

troponin has reduced the advantage that the copeptin dosage might bring to early diagnosis of ACS.[83,84]

Cyclophilin A

Cyclophilin A is a secreted protein belonging to the immunophilin family that is involved in inflammation, vascular contraction, and atherosclerosis.[85] Recent studies[86,87] show that increased plasma cyclophilin A levels are associated with more severe coronary artery disease, but the evidence until now is still inconclusive.

Cystatin C

Cystatin C is a low-molecular-weight protein acting as an endogenous inhibitor of cathepsins, which are cysteine proteases. Cystatin C is produced at a constant rate by all nucleated cells and is freely filtered by the glomerulus without secretion or active reabsorption by the tubules to the blood flow. Plasma cystatin C levels are closely related to the glomerular filtration rate, reflecting renal function, and may also be an inflammatory marker due to the proinflammatory nature of the cathepsins.[88]

Chronic kidney disease is strongly associated with the risk of new-onset CAD, as well as with the risk of death following an initial MI;[89,90] even minor changes in the glomerular filtration rate are associated with a marked increase in cardiovascular morbidity and mortality.[91,92]

The predictive value of cystatin C in patients with ACS has been evaluated in several studies.[93,94] In some studies, cystatin C has been shown to be an independent predictor of mortality,[95,96] and in some, but not all, a better marker of renal function than serum creatinine,[97] mostly because it is less dependent on body composition, age, gender, diet, and physiologic activity.

Heart-type fatty acid binding protein

Heart-type fatty acid binding protein (HFABP, also known as mammary-derived growth factor) is a stable, relatively small protein (14–15 kDa) containing 132 amino acid residues and found in the cytoplasm of myocardial cells.[98] It is involved in lipid metabolism by transporting long-chain fatty acids from the cell membrane to the mitochondria for oxidation. This protein is abundantly expressed in almost all tissues and is encoded by nine separate genes.[99]

HFABP dosage has been developed as a quantitative and qualitative assay. The first demonstration of its potential utility in the diagnosis of ischemic heart disease was published in the early 1990s, when two groups of researchers confirmed that the concentration of this novel marker was significantly and rapidly increased after an acute MI.[100,101] Its small size and hydrophilicity facilitate rapid diffusion through the interstitial space, appearing within 90 minutes

Table 1 Brief summary of the main biomarkers for ACS diagnosis currently under investigation

Biomarker	Pros	Cons
Troponin	Earlier diagnosis of ACS	May be elevated in other clinical
	Diagnosis of other causes of cardiac injury	conditions not related to ACS
Adiponectin	Role not yet fully elucidated	
BNP	Good as prognostic marker in ACS	Not useful as diagnostic marker in ACS
Cathepsins	Useful in the evaluation of cardiac remodeling after AMI	Not useful as diagnostic markers in ACS
CD40 ligand	Role not yet fully elucidated	Not useful as diagnostic marker in ACS
		Contrasting evidence as prognostic biomarker of atherothrombotic risk
CK-MB	Early release pattern after cardiac injury	Poor specificity
	Useful if troponin unavailable	
Copeptin	Early release pattern	Not useful when used alone
	Good as a prognostic marker	
Cyclophilin A	Role not yet fully elucidated	
Cystatin C	Predictive of mortality in ACS	Not useful as diagnostic marker in ACS
HFABP	Early release pattern	Not superior to troponin in ACS diagnosis
	Cardiac specificity	
IsMA	May be useful in conjunction with other markers	Insufficient sensitivity and specificity when used alone
Myoglobin	Early release pattern	Poor specificity
		Elevated in renal insufficiency
PAPP-A	Good as prognostic marker in ACS	Not useful as diagnostic marker in ACS

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; BNP, brain natriuretic peptide; CK MB, creatine kinase MB; HFABP, heart-type fatty acid binding protein; IsMA, ischemia-modified albumin; PAPP-A, pregnancy-associated plasma protein-A.

and peaking within 6 hours of symptom onset.[102,103] The early release, in conjunction with relative cardiac tissue specificity, makes it an ideal candidate for both early assessment and ruling out of acute MI and assessment of recurrent infarction; furthermore, it has performed better than myoglobin for early diagnosis of MI.[104,105] Several studies have shown its potential as a sensitive biomarker for early detection of MI as well as its prognostic utility in risk stratification of patients affected by ACS.[106]

However the diagnostic power of this marker is not superior to that of troponin immunoassays, despite its better sensitivity in patients arriving at the emergency department within 4 hours of onset of symptoms.[107–109] Lippi et al[110] found that addition of HFABP to a conventional troponin immunoassay could improve its sensitivity at the expense of a lower specificity. However, as shown in other studies,[111,112] HFABP does not seem to improve diagnostic accuracy when added to a current-generation troponin assay, although their combination provides a higher negative predictive value in early presenters. In conclusion, further larger studies are needed to assess the diagnostic power of HFABP when used in combination with the new high-sensitivity cardiac troponin immunoassays for early diagnosis/rule out of ACS.

Ischemia-modified albumin

Albumin is a plasma protein produced by hepatocytes, and is the most important protein regulating blood oncotic pressure and in the transport of several molecules and ions. It has been shown that, during acute myocardial ischemia, the N-terminal site of serum albumin is altered by free radicals, reducing its binding capacity, and this reduction is the basis of the albumin cobalt-binding test for laboratory determination of ischemia-modified albumin (IsMA). However, albumin can also be modified by hypoxia and acidosis, all of which can occur from oxidative tissue stress found in many other conditions.[113,114]

In 2007, Lee et al[115] indicated a great negative predictive value for ACS compared with the combined use of myoglobin, CK-MB, and cardiac troponin T. Zhong et al[116] studied IsMA in patients with stable atherosclerotic heart disease, showing a high correlation with severity of myocardial ischemia and a high predictive value. Baysal et al[117] found a significant association between IsMA and cardiovascular risk factors in obese children and adolescents, suggesting IsMA as an indirect marker of metabolic syndrome.

Several studies showed that levels of IsMA are much higher in patients with acute ischemia than those without, so

from 2006 a meta-analysis by Peacock et al[118] was a starting point for assessment of IsMA to rule out ACS patients. Subsequent studies found a high level of IsMA on the first day of ACS showing a high correlation, but obviously making its use for early ACS diagnosis in the emergency department setting not possible[119,120] because its sensitivity and specificity is insufficient to compete by itself with other current markers. However, IsMA combined with another more specific marker, such as cardiac troponin T, could become an important prognostic tool in clinical practice if it is supported by future studies.

PAPP-A

Pregnancy-associated plasma protein-A (PAPP-A) is zinc-binding metalloproteinase.[121] Originally identified in pregnant women, in whom it is produced in the placenta, PAPP-A is also produced by non-placental cell types such as vascular endothelial cells and fibroblasts. This enzyme cleaves insulin-like growth factor binding protein-4 from insulin-like growth factor-1, a regulatory protein in cell proliferation and metabolism, and it could play a role in the structural changes correlated with heart remodeling after MI.

In the past it was used in routine prenatal diagnosis of Down syndrome, but in the last decade, after the first demonstration of PAPP-A expression in ruptured plaques,[122] interest has shifted to the correlation between serum levels of circulating PAPP-A and disease associated with plaque destabilization.[123,124] PAPP-A showed a good correlation with risk stratification[125] and adverse cardiac events in ACS patients,[126] with a release pattern between 2 and 30 hours after cell damage.[127] An extensive meta-analysis by Long et al[128] involving 14 studies of PAPP-A and ACS suggested that a higher level of PAPP-A could indicate a moderate increase in the long-term risk of adverse cardiovascular outcomes, supporting its further investigation as a valuable prognostic predictor in ACS.

Inflammatory markers

Starting from the guiding concept that coronary artery disease is an inflammatory process, many inflammatory markers have been proposed as ACS markers over time.[129] Most of these studies have investigated C-reactive protein, myeloperoxidase, and fibrinogen.[130] Some studies evaluated serum immunoglobulin concentration as ACS biomarker. Immunoglobulin G concentration, for its early detection after MI, seemed to be the most promising marker.[131] Unfortunately, the newer markers (immunoglobulin G concentration, myeloperoxidase[132]), like the older ones

(fibrinogen, C-reactive protein,[133] interleukin-6[134]), have the same limitations. Inflammatory markers are not specific for ACS, and any coexisting chronic disease could modify the basal body inflammatory level, resulting in very low specificity.[135] Because of these characteristics, all these markers of inflammation showed no added value in early diagnosis of MI. On the other hand, because of their sensitivity these markers have been proposed as prognostic and evolution-monitoring markers.[136]

Conclusion

Over the years, many markers have supported and helped the physician to juggle the diverse signs and symptoms of ACS. Several biomarkers of ACS have been investigated, but most still require validation in further studies.[137] On April 15, 2000, new players in the diagnosis of MI, ie, the cardiac troponins, entered the scene with a consensus document from The Joint European Society of Cardiology and American College of Cardiology Committee,[138] surpassing all markers available until then. Since that time, many studies have investigated cardiac troponin and the behavior of new high-sensitivity cardiac troponin so that, due to their high sensitivity and specificity (62% and 89%, respectively), they are the current reference for diagnosis of ACS. At present, there is no evidence for the clinical use of any other marker used on its own.[139] Of all above-mentioned biomarkers, PAPP-A, IsMA, and HFABP in particular seem to be the most promising markers under investigation for their possible usefulness in an emergency department setting for early diagnosis of ACS. In the out-of-hospital setting, on the other hand, a multimarker approach could be the future of research by simultaneously exploiting point-of-care technology[140,141] to achieve the highest sensitivity in a rule out-based emergency department strategy.

Disclosure

The authors confirm that there is no conflict of interest with any financial organization regarding the material discussed in this paper.

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