sciendo

Journal of Cardiovascular Emergencies 2022
DOI: 10.2478/jce-2022-0012

REVIEW

Cardiac Biomarkers in 2022 – a Vital Tool for Emergency Care

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ABSTRACT

The role of cardiac biomarkers in diagnosing acute myocardial infarction is undoubted. In the 2020 guidelines of the European Society of Cardiology, the measurement of cardiac peptides to gain prognostic information has a class IIa indication in all patients with ACS. In emergency care, ruling out a non-ST elevation myocardial infarction requires documentation of normal levels of cardiac biomarkers, which remain stable or have very small variations within several hours. This review aims to summarize the current knowledge and recent progresses in the field of cardiac biomarker discovery, from their routine use in emergency rooms to their prognostic roles in modern risk assessment tools. Integrated approaches combining cardiac troponin with other biomarkers of ventricular dysfunction or inflammation, or with modern cardiac imaging in emergency care are also presented, as well as the role of modern algorithms for serial troponin measurement in the modern management of emergency departments.

Keywords: cardiac biomarkers, emergency cardiovascular care, acute coronary syndromes

ARTICLE HISTORY

Received: September 20, 2022
Accepted: September 27, 2022

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INTRODUCTION

Chest pain represents the second most common cause for presentation in the ED, and more than 90% of emergency hospitals report a significant overcrowding of their emergency departments (EDs). It is well known that 9 in 10 patients presenting with chest pain do not have an acute coronary syndrome (ACS). Therefore, the identification of rapid and effective protocols that may rule out ACS, allowing an early and safe discharge of patients with chest pain and no ACS, is of crucial importance in any healthcare system. The criteria used today to establish a diagnosis of acute myocardial infarction (AMI) is based on the identification of abnormal cardiac biomarkers in the evidence of acute myocardial ischemia.[1,2]

While in ST-elevation myocardial infarction (STEMI) the diagnosis is very facile, relying on ST elevation on surface ECG, the situation is different in non-STEMI type ACS. In real life, a STEMI patient is referred to urgent percutaneous coronary intervention (PCI) without waiting for the results of cardiac biomarkers, since every minute counts and any delay may lead to increase in mortality. On the contrary, the diagnosis of non-STEMI requires validation by increase in myocardial enzymes, most commonly cardiac troponin I (cTnI) or cardiac troponin T (cTnT). At the same time, since in non-STEMI the ECG aspect presents a large variability,

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ruling out a non-STEMI requires documentation of normal levels of cardiac enzymes, which remain stable or have very small variations within several hours.

According to the 2020 guidelines of the European Society of Cardiology (ESC), measuring cardiac peptides to gain prognostic information has a class IIa indication in patients with ACS.[1]

CTN ELEVATION IN THE ED

Several aspects have been debated in the last years in relation to the clinical use of cardiac biomarkers. First, the selection of cTnT versus cTnI has been tested by many studies. Second, the introduction of high-sensitivity assays for the detection of small changes of cTn has led to a significant increase in the detection power based on troponin values. Third, the timing of serial measurements is without any doubt an issue of major importance for the early detection of troponin increase.[3]

The main difference between cTnI and cTnT is that although both are parts of the cTn protein complex, cTnI binds to actin to form the actin-tropomyosin complex, while cTnT binds to tropomyosin to form the troponin-tropomyosin complex. The level at which AMI is likely is different for the two types of cTn, the limit being established at 0.1 for cTnT and 1.0 for cTnI.[4]

At the same time, it should be remembered that elevated levels of cTn may also result from various conditions different from ACS such as heart failure (HF), hypoxemia, hypotension, shock, kidney disease, or ventricular arrythmia. Identification of a rise-and-fall pattern, typical for acute myocardial ischemia, is required in order to establish the diagnosis of myocardial infarction based on increased Tn levels. Opposite to the AMI pattern, cTn increase may be associated with HF, kidney disease, or other comorbidities. In these cases, cTn presents constantly and mild to moderately increased levels, with no or very limited variations in time. The rising and/or falling cTn levels may differentiate acute myocardial injury from chronic cardiomyocyte damage, the likelihood of AMI being directly associated with the amplitude of cTn change.[5–7]

CARDIAC TROPONINS AND HIGH-SENSITIVITY FORMS

The introduction of high-sensitivity assays has led to the ability to detect circulating levels of cTn more precisely than conventional ones. Hs-cTn assays are able to detect circulating cTn even in patients with normal levels of cardiac biomarkers, which has a strong impact on the ability to detect NSTEMI and is particularly important in the case of very low variations.

Currently, the preferred biomarker indicated by the ESC guidelines, ACC/AHA guidelines, and other international societies for the diagnosis of AMI is hs-cardiac TnT. The use of hs-cTnT may lead to better diagnosis of special conditions such as type 2 myocardial infarction or periprocedural MI.[8,9]

ALTERNATIVE BIOMARKERS OF MYOCARDIAL INJURY

Copeptin seems to be a promising biomarker for the detection of ACS, which is associated with increased acute hemodynamic stress. Copeptin is released into circulation immediately after the occurrence of AMI, within a few minutes after the acute obstruction of the coronary artery, being therefore superior to troponin, which is increased 3 to 6 hours after symptoms onset. Increased serum levels of copeptin are detectable in patients with AMI at presentation to the ED, already in the first minutes after AMI onset.[10]

In the BIC-8 trial, a dual biomarker strategy based on determination of copeptin and hs-cTnT at presentation was as efficient as the standard strategy based on serial cTn to predict major adverse cardiac events (MACE) at 30 days (4.34% vs. 4.27%), suggesting that copeptin combined with cTn at presentation may replace the serial determination of cTn with retesting at 3 hours or later, as recommended by the standard protocol today.[11]

Elseidy *et al*. also reported that negative copeptin combined with negative hs-cTn testing in patients at low-to-intermediate risk of ACS may allow a rapid and safe discharge from the ED, effectively ruling out the non-STEMI type of ACSs.[12]

Another relatively new biomarker is dipeptidyl peptidase 3 (DDP-3), which is associated with cardiogenic shock, sepsis, and burns, being related to hemodynamic instability. It seems that this biomarker may serve as an important indicator of myocardial depression and predicts left ventricular dysfunction following ACS.[13]

Other biomarkers associated with ACS, recently described but rarely used in practice, are endothelial cell-specific molecule-1, intercellular adhesion molecule-1, and pregnancy-associated plasma protein A.[14]

CURRENT METHODS TO DETERMINE CARDIAC TROPONIN

The method used for the determination of cardiac troponin may be variable, and several new-generation equip-

ment have been introduced in the last years for the determination of hs-cTn T or I.[15,16] The analytical agreement between the two types of Tn (I and T) seems to be high, one study reporting an agreement coefficient of 95.2%.[17] In a study on 5,377 patients presenting to the ED with chest pain and suspected ACS, the implementation of hs-cTnT determination increased the rates of direct discharge from the ED, without any increase in mortality.[18] A very pragmatic approach results from the use of Atellica VTLi Patient-side immunoassay analyzer, which showed equivalent results for all types of blood sampled, including capillary blood, which may represent a significant advantage in the ED.[19]

According to the currently published data, the best diagnostic performance of high-sensitivity troponin is recorded in patients with low CV risk, in whom the investigators recorded the highest specificity and negative predictive values for coronary artery disease (CAD).[20]

The diagnostic accuracy of absolute versus relative changes in Tn values was investigated by Ravanavena *et al.*, who found that absolute increase in cTn may be superior to the relative change of cTn serum values to predict evolution in patients with ACS.[21]

CCTA AND CARDIAC BIOMARKERS IN THE ED

An integrated approach of various scores and diagnostic tests was investigated in a study that included risk scores, copeptin, and cardiac computed tomography angiography (CCTA). The investigators found that patients with increased copeptin levels were older and more likely to be admitted to the hospital with a diagnosis of ACS. At the same time, a combined approach including CCTA and copeptin provides the highest power for ruling out an ACS (AUC 0.772, p <0.001), superior to hc-sTn, risk scores, or any other test.[22]

In another study, patients with suspected ACS in whom AMI has been excluded based on hs-cTn values, underwent CCTA following AMI rule-out, to identify the presence of CAD. The authors demonstrated that CAD was 3 times more likely in patients who had slightly elevated levels of hs-cTnI compared to those with low values of serum hs-cTnI, indicating that CCTA added to routine hs-TnI determination could improve the diagnosis of chronic coronary syndromes in patients presenting to the ED for chest pain.[23]

However, in another study published recently, Wang *et al.* demonstrated that the cardiac troponin at presentation had no significant effect on the clinical impact of early CCTA in intermediate-risk patients presenting to the ED for chest pain. The rate of noninvasive and invasive testing, coronary revascularization, and the primary outcomes were not significantly influenced by the values of cardiac troponin (p for interaction 0.33 for noninvasive test, 0.33 for invasive tests, and 0.57 for PCI). At the same time, patients with elevated cTn values who had a higher GRACE score (1,323 vs. 91, p <0.001) were more likely to need revascularization (47% vs. 15%, p <0.001) and had a significantly higher rate of primary outcome (8% vs. 3%, p = 0.007), suggesting the superiority of cardiac troponin over imaging tests in the ED.[24]

The RAPID-CTCA RCT study investigated the role of early CCTA in patients presenting to the ED for chest pain and suspected ACS, and failed to demonstrate a significant reduction of the revascularization rates, ACS therapies, or preventative therapies at discharge following early CCTA in patients with elevated cTn.[25] This underlines the superiority of cTn as a first-line diagnostic test for triage of patients with suspected ACS in the ED, elevated cTn levels being sufficient for establishing the diagnosis in the absence of other expensive techniques.

A meta-analysis published by Mehta *et al.* including 21 studies showed that patients with chest pain, negative stress test, and CCTA showing no significant stenosis (no obstruction >50% in any coronary artery) may be discharged safely if their Tn values are not elevated, given the low risk of MACE in this population.[26]

Another interesting imaging approach results from the association between cTn sampling and CMR in cases with unclear diagnosis. For instance, the role of a combined approach including troponin and CMR for elucidating MINOCA etiology has been tested in another recently published study, which demonstrated that CMR performed <14 days from presentation may elucidate the diagnosis of MINOCA, especially when peak troponin is >211 ng/L (94% diagnostic yield compared with 53% when peak troponin was <211 ng/L).[27]

ARTIFICIAL INTELLIGENCE IN THE ED

The role of artificial intelligence (AI) for the early diagnosis of ACSs is emerging, since recent studies identified the superiority of machine learning approaches for establishing the risk of ACS based on prediction models, validating the algorithms against real-life data.[28] In a recent study published this year, a prediction model based on age, non-STEMI type, Killip class, and biomarkers such as cTnI, NT-proBNP, D-dimers, or creatin-kinase was useful for predicting the risk of in-hospital death, with an AUC between 0.884 and 0.913 according to the model used.[29]

Another study which tested a machine learning algorithm for estimating the likelihood of AMI validated the role of these AI-based approaches, reporting the occurrence of cardiovascular death or AMI in 17.6% of patients classified by the algorithm as high-risk, compared to only 1.5% in those classified as low-risk (p <0.0001).[30]

COMBINED BIOMARKER APPROACH IN EMERGENCY CARE – NATRIURETIC PEPTIDES AND TROPONIN

The prognostic power of a combined approach including natriuretic peptides and cTn has been extensively studied. Patients with chronic HF present a constant increase in the level of hs-cTn, which seems to be directly associated with the evolution of ventricular dysfunction.[31,32] The GUIDER score, including glucose, cTn for injury detection, and NT-proBNP for ventricular dysfunction, was proposed for risk stratification in patients with HF. The authors of a recent study demonstrated that the GUIDER score has a sensitivity of 100% and specificity of >92% for the primary outcome.[33]

Since the majority of patients with acute HF have increased cTn values, the differentiation between ACS and acute HF may be challenging in emergency settings. In a retrospective study on patients with AHF and increased values of cTn, the authors demonstrated that the diagnosis of AMI in patients with acute HF requires higher cut-off values for hs-cTn than in the overall population with ACS.[34]

Another study evaluated the relationship between cTn elevation and clinical outcomes in patients with acute HF presenting to the ED and found no significant association between cTn and the primary outcome consisting in time to 30-day cardiovascular death or HF events, suggesting that patients with acute HF and no ACS may be safely discharged even in the presence of elevated cTn.[35]

The implementation of hs-cTn assays resulted in an increase of diagnosis of HF (increase of 2.1%, p <0.001) or atrial arrythmia (increase of 0.9%, p <0.001), in parallel with an increased likelihood of receiving stress test (increase of 2.3%, p <0.001).[36]

On the other hand, NT-proBNP has also been demonstrated to be a reliable biomarker associated with the prognosis of ACS. In a study on 3,986 patients with ACS, NT-proBNP values were significantly correlated with peak values of cTn (r = 0.4) and with the risk of composite MACE, all-cause death, and nonfatal myocardial infarction. Also, adding NT-proBNP to the TIMI risk score significantly improved the prediction power for cardiovascular death and HF requiring hospitalization.[37] In a study on 1,756 patients, Galvani *et al.* demonstrated that the measurement of NT-proBNP on admission in patients with ACS may improve early risk stratification, mortality being significantly higher in the fourth quartile compared to the first three quartiles.[38] In a recent study, Lu *et al.* demonstrated that the combination of NT-proBNP and D-dimer improved the prognostic value of GRACE score for all-cause death and MACE.[39]

A large study comparing cTn levels and ventricular dysfunction in patients with STEMI identified a weak but significant association between the magnitude of myocardial injury, expressed by cTn levels, and the extension of ventricular dysfunction, expressed by NT-proBNP. In this study, cTn had a cut-off of 3.4 ng/L, a sensitivity of 56%, and a specificity of 65% for predicting LV dysfunction in STEMI patients.[40]

COMBINED BIOMARKER APPROACH IN EMERGENCY CARE – INFLAMMATION AND CARDIAC INJURY

An interesting approach of biomarker-directed research is related to the implementation of a C-reactive protein (CRP) test to detect inflammation-prone STEMI patients, since elevated CRP levels during an ACS may be associated with worse outcomes caused by the increased systemic inflammatory response. In a retrospective analysis on more than 1,000 patients with AMI, Brzezinski *et al.* showed that patients with high CRP values had higher 30-day and all-cause mortality (14.4% vs. 2.7%), independent of their cTn levels, with the highest mortality recorded in the subgroup of patients with significantly increased CRP and cTn. This suggests the potential role of a combined determination of inflammatory and injury biomarkers to identify patients who could benefit from early anti-inflammatory therapy added to the standard of care.[41] Another large retrospective study tested the same hypothesis on 257,948 patients with suspected ACS who had cTn and hs-CRP measurement, and found that mildly elevated hs-CRP (up to 15 mg/L) is associated with worse outcomes, independent on the value of cTn. This further supports the recommendation to add anti-inflammatory therapy in patients with high inflammatory risk.[42]

In a small prospective study including patients with ACS versus patients with stable angina, those with ACS presented a significant correlation between hs-cTn and inflammatory biomarkers (r = 0.5 for CRP and r = 0.51 for neutrophil/lymphocyte ratio), indicating that inflammatory biomarkers are useful for risk stratification in ACS patients.[43]

CARDIAC TROPONIN AND COMORBIDITIES

Comorbidities play a significant role in the evolution of patients with ACS and may also influence the values and evolution of cTn. A study on more than 5,000 patients demonstrated that in the presence of sepsis, the optimal cut-off of cTnI for non-STEMI diagnosis was 300 ng/L, and cTn levels were significantly correlated with GRACE scores, with comparable predictive power for 6-month mortality.[44]

In patients with kidney disease, the utility of hs-Tn for the diagnosis of AMI is altered by the constant increase in the serum levels of cardiac Tn. In the High-STEACS study, the implementation of hs-Tn testing in the management of patients with kidney disease increased the diagnosis of AMI from 12.4% to 17.8%.[45] Another study on patients with end-stage renal disease from a hemodialysis center identified increased levels of Tn in 99% of patients.[46] A similar study on 143 patients with chronic kidney disease and no history of AMI identified a significant association between increased cTn on one hand, and left ventricular hypertrophy and decreased renal function and age on the other hand.[47]

Atrial fibrillation is another comorbidity associated with increased cardiac Tn. A report from the ESC-EHRA EORP registry on atrial fibrillation describes elevated cTn levels in 31.9% of patients with atrial fibrillation, and elevated cTn levels were associated with a higher incidence of MACE and all-cause death.[48]

A study published very recently tested the efficacy of the ESC 0/1 h algorithm in patients with prior coronary bypass and identified a good sensitivity/specificity or the rule-in/rule-out protocols (100% and 93.5%), but with lower efficacy in this study population compared to the general population (52% vs. 74%, p <0.01).[49]

A study published by Ticinesi *et al*. investigated the role of hs-cTn increase in elderly population presenting to the ED for chest pain and suspected AMI. It should be remembered that old patients are usually frail and frequently present elevated levels of hs-cTnI, which makes it difficult to interpret an elevated hs-cTnI in the ED in this group of patients. In this study conducted on 268 geriatric patients with a median age of 85, hs-cTnI was elevated in 71% of cases; however, AMI was present in only 4.5% of cases. This indicates that elevated values of biomarkers associated with ACS should be interpreted carefully in patients with frailty, advanced age, and multiple comorbidities, since increased Tn levels do not necessarily reflect an acute myocardial injury, but may be associated with other comorbidities which are quite frequent at this age.[50]

CARDIAC TROPONIN IN THE COVID ERA

The recent COVID-19 pandemic has opened new applications for cTn testing in the ED, and COVID patients with elevated cTn were considered at high risk for developing a severe form of systemic infection.[51] While many studies documented a direct relationship between COVID mortality and cTn values at presentation, little is known about the combined prognostic role of natriuretic peptides and cTn in this population. This hypothesis was tested by Iorio *et al*., who demonstrated that patients with elevated NT-proBNP and cTn levels had a higher risk of death at 14 days (HR 2.94, p = 0.009), and patients with high NT-proBNP had a higher risk of death even in the presence of normal cTn values (HR 2.86, p = 0.016). Also, they found that the cut-off value used for NT-proBNP for diagnosing acute HF was also reliable to predict a severe form of COVID-19.[52]

The association between COVID-19 and AMI may represent a lethal combination. In a study on 397 COVID patients with AMI, peak cTn values were not significantly different between COVID and non-COVID patients (1.62 ng/L vs. 1.47 ng/L), but the alteration of ventricular function was more expressed in COVID patients. Those with concomitant COVID-19 and AMI had more frequent HF (51.16% vs. 27.84%, p = 0.03), in parallel with a significantly higher need of extracorporeal membrane oxygenation (ECMO) implantation (2.38 % vs. 1.26%). At the same time, ventricular fibrillation and resuscitation were more frequent in the COVID group (11.6% vs. 6.8% for VF, and 23.2% vs. 10.08% for resuscitation).[53]

THE PROGNOSTIC ROLE OF ELEVATED CARDIAC TROPONIN

The prognostic role of elevated cTn or hs-cTn was tested in a large number of studies or clinical trials. In a study including 12,869 patients presented to the ED and with serial determinations of hs-cTn, out of which 25% died in a median follow-up of 2.3 years, patients with a temporal increase in hs-cTn had a significantly higher adjusted all-cause and CV mortality (HR 4.21, 95% CI 3.55 to 5.00 for all-cause mortality, and HR 5.08, 95% CI 3.73 to 6.92 for CV mortality), with almost 3-fold higher adjusted risk of HF, indicating that patients with the highest risk of death are those with myocardial injury associated with a significant increase of hs-cTnT.[54]

The variation of hs-cTn in stable patients has been also demonstrated to play a role in the future evolution of CV patients. In a study conducted by Biener *et al*., changes in

Tn levels exceeding a minimal pre-specified value were associated with a 5.5-fold increased risk for all-cause mortality and a 2.4-fold increased risk for nonfatal myocardial infarction and stroke.[55]

The prognostic role of hs-cTn is also underlined by the study of Chapman *et al.*, who showed that in patients with clinical suspicion of ACS, a serum concentration of hs-TnI below 5 ng/L identifies the subset of patients with low risk of AMI and cardiovascular death at 30 days.[56]

The CHOPIN study enrolled 1,982 patients presenting to the ED for chest pain, in whom cTnI elevation was analyzed. The analysis showed that in these patients, cTnI elevation was associated with a worse prognosis if the chest pain was not attributable to an ACS.[57]

A second peak of Tn in sometimes recorded in the early post-AMI period; however, it does not seem to be reflected in a worse outcome, therefore the clinical significance of this finding remains unclear.[58]

CURRENT ALGORITHMS FOR TROPONIN-BASED AMI RULE-IN/RULE-OUT IN THE ED

The ESC recommends clear algorithms for serial determination of cTn levels in order to detect the rise and fall pattern of cTn change and to safely rule out ACS in case of normal values that persist after repeated measurements.[1] In a study published by Gimenez *et al.* in 2015, an algorithm incorporating baseline values of hs-cTnI and their change in one hour may safely confirm or exclude an AMI in 70% of patients with clinical suspicion of AMI.[59] Similarly, another study published in the JACC by Tverenbold *et al.* reported that an algorithm using hs-cTnI and its variation within one hour allows safe discharge of patients with clinical suspicion of AMI.[60]

The performance of the rapid 0/1 h algorithm in different studies was analyzed in a meta-analysis by Nomura *et al.*, who reported, after carefully reviewing 10 observational databases, that the ESC 0/1 h algorithm using hs-cTn has a pooled sensitivity of 99.3% and a pooled specificity of 91.7% for the detection of non-STEMI type of AMI.[61] Another study investigated the effectiveness of such an accelerated protocol in patients discharged despite of modest elevation of hs-Tn. In more than 10,000 patients discharged according to this accelerated protocol, only 0.29% had MACE during a 30-day follow-up, but the rate of MACE was significantly higher in those discharged despite having a HEART risk score higher than 4.[62]

In the 2020 ESCV guidelines, an alternative to the 0/1 h algorithm may be represented by the 0/2 h algorithm with blood sampling at baseline and repeated at 2 h, if a method test is available. According to a recent study by van den Berg *et al.*, the 0/2 h algorithm demonstrated the highest sensitivity for the diagnosis of NSTEMI-type ACS, superior to the High-STEACS algorithm and the ESC 0/3 h algorithm (98.2% vs. 93.7% vs. 79.3% sensitivity).[63]

The 0/3 h algorithm may be also used in cases when the 0/1 h algorithm failed to diagnose an AMI, the clinical suspicion of AMI remains high, and the etiology of chest pain is not elucidated. A survey conducted in Germany's certified EDs showed that 77% of ED practitioners use the ESC 0/3 h hs-Tn protocol, while only 20% use the ESC 0/1 h hs-Tn protocol by default.[64]

EFFECTIVENESS OF CTN ALGORITHMS IN EMERGENCY CARE

The administrative impact of cTn may be extremely significant, especially in very well-organized medical systems. In a study published by Hariri *et al.*, 1,385 patients with non-STEMI ACS were discharged the same day after nonelective PCI following a decisional algorithm that included age, radial access, and cTn value at presentation, and found no difference in terms of 30-day mortality and readmission between patients discharged the same day and those discharged the next day.[65]

The determination of cTn is particularly useful for ruling out myocardial infarction, allowing safe early discharge and reduction of the overcrowdedness of the EDs.[66] In a study including 10,315 consecutive patients, the implementation of a strategy of ruling out MI if hs-cTnT concentrations were <5 ng/L at presentation and symptoms were present for >3 hours, or cTn <5 ng/L and unchanged at 3 hours, led to a significant reduction in the duration of stay in the ED, from 534 min before implementation to 390 min after implementation ($p < 0.0001$), without any negative impact on patient safety.[67]

In another study which compared new algorithms with the standard ESC-recommended algorithm used for ruling out NSTEMI based on cTn measurements, investigators found that a 0-1 h/0-3 h algorithm based on low baseline level and low variation had superior clinical sensitivity than the ESC algorithm: 95% vs. 65% for hs-cTnT and 87% vs. 64% for hs-cTnI.[68]

The RAPID-TnT trial aimed to investigate the economic impact of the accelerated protocol for 0/1 h testing of hs-cTnT and found that despite an initial superior efficiency of the accelerated protocol, it led to no significant reduction of resource utilization compared to the standard 0/3 h protocol. Despite reducing the length of stay in the ED by

0.62 h per patient, the costs recorded were higher in the 0/1 h protocol arm by 472.49 USD per patient.[69]

In a controlled observational study conducted before and after the implementation of the 0/1 h algorithm, the median time interval between serial troponin tests decreased from 4.7 hours to 2.3 hours, but this was not accompanied by a reduction in median provider-to-disposition decision time, which remained almost unchanged: 4.7 hours before and 4.8 hours after the implementation of the new algorithm.[70]

In an attempt to investigate the clinical feasibility of the ESC 2020 rapid 0/1 h algorithm, Couch *et al.* found many practical limitations of achieving the 1 h target for the repeated Tn sampling, mainly related to the need for the second blood draw prior to obtaining the results of the first blood draw in the real-life settings of the ED.[71]

BIOMARKER-BASED RISK SCORES IN PATIENTS WITH ACS

Different risk scores were proposed for the stratification of risk in patients with ACS, and most of them include cardiac biomarkers as a cornerstone for predicting ACS-associated risk.[24] The GRACE score is one of the most well-known scores utilized in acute cardiac care, predicting the risk associated with an ACS and influencing management decision in patients with non-STEMI. In non-STEMI patients, therapeutic decision in favor of immediate, early, or late referral to PCI is largely guided by the severity of non-STEMI, which is also reflected by the GRACE score.

The role of such scoring systems is mainly related to the possibility to stratify the risk associated to patient condition in order to safely discharge the patient as soon as possible. Berikol *et al.* developed a risk score to decide about the early discharge of low-risk patients and found that 2-hour hs-cTnI had a high negative predictive value as a risk assessment instrument, patients with negative hs-cTnI at 2 hours having low risk and being amenable for early discharge.[72]

A risk scoring model was also proposed to differentiate obstructive coronary artery disease from coronary spasm, score which included cTn values, age, diabetes mellitus, natriuretic peptides, neutrophil-to-lymphocyte ratio, and LDL-cholesterol.[73]

The HEART score is one of the most frequently used scores in the USA and includes history, ECG, age, risk factors, and cTn levels for predicting the severity of an ACS. A comparison between the HEART score and the SVEAT score (symptoms, history of vascular disease, electrocardiography, age, and troponin) was investigated in a recent study by Antwi-Amoabeng *et al.*, who found that the SVEAT score is superior to the HEART score as a risk stratification tool, with an AUC of 0.88 for the SVEAT score compared to an AUC of 0.79 for the HEART score ($p = 0.003$), and with a SVEAT score lower than 4 being able to predict 30-day MACE with an OR of 1.52.[74]

Another study tested the effectiveness of the HEART score for discharging patients with chest pain as quickly as possible from the ED and found that using only biological variables, such as hs-cTn, is more effective than any other approach to identify patients who may be safely discharged.[75]

Interestingly, physicians used to the HEART score demonstrated limited willingness to discharge early from the ED patients classified as having low risk by the ESC algorithm but moderate risk by the HEART score.[76]

A modified HEART score, integrating capillary cTn determined using a new point-of-care test, was able to rule out ACS in patients presenting to the ED for chest pain, with a sensitivity of 97.0% and specificity of 97.6%, opening the route for point-of-care devices for Tn measurement.[77]

However, several scores excluding cTn have been also proposed to establish the safety of early discharge in patients presenting to the ED for chest pain, in an attempt to save the costs related to cTn measurement. These include the HE-MACS (History and Electrocardiogram-only Manchester Acute Coronary Syndromes decision aid) and the HEAR (history, ECG, age, risk factors) scores, which still need further validation for implementation in clinical algorithm.[78]

CARDIAC TROPONIN AND RISK STRATIFICATION

A risk stratification algorithm was proposed for better resource management in the ED. The RISTRA-ACS (risk stratification for acute coronary syndrome) algorithm is a graded coronary risk stratification algorithm, the implementation of which has led to better resource utilization in the ED, including more judicious use of cTn testing. According to a controlled cohort study by Mark *et al.*, cardiac biomarker testing decreased at 30 days among patients with low risk of MACE and increased at 30 days among patients with high risk of MACE following the implementation of the RISTRA-ACS algorithm.[79]

CONCLUSIONS

In conclusion, the measurement of cTn is an essential tool in the ED, particularly useful for the management of pa-

tients presenting with chest pain. The measurement of cTn may provide extremely reliable prognostic information in patients with ACS, and the serial measurement of cTn values using the ESC-recommended 0/1 h, 0/2 h, or 0/3 h algorithms may help to rule out non-STEMI type of ACS. These modern algorithms allow a fast and safe discharge from the ED after ruling out the presence of myocardial injury and should be effectively implemented in all EDs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

This research was funded by the CARDIOCOV project – "Prototype for personalized assessment of cardiovascular risk and post-Covid myocarditis based on artificial intelligence, advanced medical imaging and cloud computing" – financed by UEFISCDI PN-III-P2-2.1-PTE-2021-0450.

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