Original article

The *D*iagnosis of *A*cute *M*yocarditis in *E*mergency (DAME) score: improving diagnostics within the emergency department.

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ABSTRACT

Purpose: . The final diagnosis of myocarditis is challenging. The aim of our study was to provide the D.A.M.E. (**D**iagnosis of **A**cute **M**yocarditis in **E**mergency) Score for the fast identification of patients suffering from myocarditis at Emergency Department (ED).

Methods: . This was a multicenter, retrospective study involving three centers. All medical records from January 2010 to December 2014 reporting a final discharge diagnosis of myocarditis were considered. One hundred-four patients (mean age: 40.2±16.5 years) were enrolled. Clinical, biochemical and instrumental data were gathered. Data were analysed by means of logistic regression model and factorial analysis. A validation cohort from a fourth center was enrolled.

Results: . The final determinants of the DAME score were six: fever, chest pain, erythrocyte sedimentation rate (ESR) > 20 mm/h, C-reactive protein (hs-CRP) >3 mg/L, troponin serum levels >3 ng/L, and left ventricle ejection fraction < 50%. All of them received a specified score ranging from 0 to 4. A score > 4 was related to 75% probability of myocarditis; a final score ranging between 1 and 4 was related to 57% probability of myocarditis. ROC curve on the validation cohort (289 patients, 27 with myocarditis) demonstrated the best cut-off to be 7: AUC 0.958 (p< 0.001), sensibility: 100%, specificity: 85.11%, PPV: 40.9%, NPV: 100% (LR+: 6.72; LR-: 0.00). Logistic regression analysis revealed Odds Ratio equal to 2.83 (95% CI 1.90 – 4.20, p < 0.0001).

Conclusions: . DAME score can offer a reliable tool in ED setting for the evaluation of patients suffering from suspected myocarditis.

1. INTRODUCTION

Myocarditis is defined as an inflammatory cardiac muscular disease. The etiology is extremely heterogeneous, the causes varying from infective (bacterial, viral, etc) to non-infective (drugs, physical and biochemical agents, systemic inflammatory diseases, etc). [1] The prevalence of myocarditis is difficult to be estimated as most of them passes underdiagnosed or misdiagnosed. Dedicated, retrospective studies outlined a prevalence of 22 cases per 100,000 individual/years as incidence, [2] while autoptic studies revealed the occurrence of fatal

Abbreviations: AUC, area under the curve; BNP, brain natriuretic peptide; CMR, Cardiac magnetic resonance; ECG, electrocardiogram; ED, Emergency Department; ESR, erythrocyte sedimentation rate; hs-CRP, high sensitive C-reactive protein; hs-TnI, high sensitive Troponin I; LR, likelihood ratio; LVEF, left ventricle ejection fraction; NPV, negative predictive value; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PPV, positive predictive value; ROC, receiver-operating characteristic.

acute myocarditis in 0.46 cases per 100,000 individuals/years [3] or, at least 0.53% prevalence within an Italian sample population (i.e. 91 cases among 17,162 postmortem records derived from autopsies). [4]

The prognosis of overt myocarditis can vary from death and/or need for heart transplantation to complete recover of cardiac function. [5] Despite invasive and non-invasive prompt approaches, a 10% mortality rate at 3-year follow-up still remains. [6]

The major issue related to myocarditis management is the "early identification" of patients at the Emergency Department (ED). The acute onset of the disease, mainly characterized by fever and pulmonary symptoms, may lead to the wrong impression of a disease of other organs than the heart. This can lead to delay diagnosis or misdiagnose myocarditis. [7] As more than 3.5% of younger (< 25years old) patients suffering from myocarditis can develop heart failure in the next future, [8] the need for early detection since ED's arrival is the major goal for clinicians.

Most of the Italian EDs are not endowed with cardiac magnetic resonance (CMR) which can help physicians in diagnosing myocarditis. Dedicated scores able to give a fast overview about the possible presence of a patient suffering from myocarditis are not available. Manchester triage system and HEART score are reliable scales able to evaluate and differentiate causes of chest pain within ED. [9] The need for implementation of protocols for myocarditis detection can be considered as a useful program able to promote better evaluation of patients suffering from rare conditions such as myocarditis.

The aim of our study was to provide the D.A.M.E. (***D**iagnosis of **A**cute **M**yocarditis in the **E**mergency*) Score for the fast evaluation and identification of patients suffering from myocarditis and attending the ED.

2. MATERIALS AND METHODS

This was a multicenter, retrospective study involving three centers: the Cardiovascular Diseases Sections of the University of Bari/Bari Policlinic, Hospital San Paolo - Bari, Hospital San Martino - Genoa. All the medical records from January 2010 to December 2014 reporting a final discharge diagnosis of myocarditis were considered and reviewed by two physicians (L.G.G. and M.M.C.). The analysis of the final diagnoses led us to identify 104 patients (91 males, mean age: 40.2 ± 16.5 years, range: 19-82 years) who were discharged from the involved centers with a final diagnosis of myocarditis. Clinical, biochemical and instrumental data were gathered from the medical records and computed into a dataset for statistical analyses. Coronary angiography was performed during the index hospital stay but no biopsies were performed as the risk for biopsies outlined the benefits. None of the patients were on conditions which needed cardiac biopsies. Cardiac magnetic resonance was performed in some patients for whom myocarditis diagnosis was in doubt.

Clinical conditions were defined as following: "chest pain" as thoracic retrostenal pain, radiating to the neck, one or both upper arms, or interscapular zone; "fever" was defined as body temperature higher than 37.0°C within 30 days before hospital admission. The evaluation of electrocardiograms (ECG) at admission was performed in order to evaluate ST/T wave changes such as ST-segment elevation or depression and/or T-waves inversion.

We collected laboratory data from admission: hemoglobin, white blood cells count, high sensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and high sensitive Troponin-I (hs-TnI).

Antibodies for viral markers were identified in some cases. Although we included them into the dataset, they could not be used for the final evaluation due to missing data.

Follow-up was carried out from 30 days to five years after discharge, in order to evaluate short, mid, and long term adverse events (all-cause mortality, cardiovascular death, heart failure occurrence, myocarditis recurrence). The patients were followed up during outpatient visit or by means of direct phone calls.

The external validation phase was independently performed after the generation of DAME score. Data from 289 patients who were admitted to the Cardiology Department of the Hospital "F. Perinei" Altamura (BA), Italy from January 2018 to January 2020 were collected. *Inclusion criteria*: acute coronary syndrome-like symptoms or new onset or worsening heart failure in the absence of coronary artery disease and known causes of heart failure at ED admission; suspected diagnosis of myocarditis. The inclusion criteria were mutually exclusive. All of the patients should have an age ≥ 18 years old. *Exclusion criteria*: definite diagnosis of worsening heart failure or de-novo heart failure due to well-established causes (valvular heart diseases; cardiomyopathies; etc), pulmonary embolism, aortic dissection, and pulmonary diseases. The diagnosis of myocarditis was performed on the basis of coronary angiography and cardiac magnetic resonance. No cardiac biopsies had been performed.

Informed consent was obtained from all included patients at admission into ward. The study was performed in agreement with Declaration of Helsinki guidelines and received the approval by the local Ethic Committee.

2.1. Echocardiographic evaluations

All patients underwent echocardiographic assessment as routine evaluation in suspected myocarditis. In agreement with international guidelines, [10] transthoracic echocardiography was performed in order to evaluate: left ventricular end-diastolic volume, left ventricle end-systolic volume, myocardial walls contractility/kinetics, left ventricle ejection fraction (LVEF, calculated by means of modified biplane Simpson's method). [11]

Echo color Doppler was adopted in order to quantify and estimate the severity of valvular regurgitations. [10]

3. STATISTICAL ANALYSIS

The analyses were made using the Statistical Package for Social Science (SPSS) software, version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean and standard deviation. Categorical variables were reported as frequency and percentage. Data were computed and analysed by means of two models: logistic regression analysis and factorial analysis. Logistic regression analysis allowed the selection of the most statistically significant variables for the definition of the score. Clinical and instrumental characteristics of the patients underwent univariate regression analysis. A correlation matrix for analysis of collinearity was adopted. Continuous variables were converted into categorical variables for practical purposes. Variables with P-values ≤0.10 entered a logistic regression model in order to identify the candidates for final inclusion into the DAME score. The factorial analysis was applied to the variables derived from the logistic regression analysis in order to obtain the determinants of the DAME score.

In particular, the final variables which were included in the model after statistical analysis were the following: fever, viral prodromes, chest pain, ECG, gender, white cells blood count.

The Kaiser Meyer Olkin index was used in order to evaluate the reproducibility of the model. We obtained a Kaiser Meyer Olkin index value equal to 0.57 (values higher than 0.5 meant good adaptation of the model). The model is able to explain the 62.7% of the overall variability.

The areas under the receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of the DAME score in the validation cohort as well as corresponding specificity, sensitivity, accuracy, and positive and negative predictive value (PPV and NPV, respectively). The optimal cut-off was obtained from the greatest sum of sensitivity and specificity. The Youden index method was adopted. Positive and negative likelihood ratio (LR+ and LR-) were calculated. [12]

Finally, P-values below 0.05 were defined as statistically significant for the overall analysis.

4. RESULTS

Table 1 gathered the characteristics of the derivative study population. Most of patient showed chest pain (90 patients, 86% of the population) and fever (61 patients, 58% of the population) as first expression of the disease. Tachycardia and exertional dyspnea were the second most frequent conditions at admission. Finally, acute onset of heart failure or syncope occurred at patients' admission. According to laboratory findings, we observed an increase in troponins, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), hs-CRP, ESR, plasma leukocytes. Most of patients (71%) showed pathological modifications in ST-T segment, while only mild impairment in left ventricle ejection fraction was registered (53.6 ±9.1%) (table 1).

All the characteristics in table 1 were all computed into the statistical model in order to achieve the identification of those really related to myocarditis identification. We applied univariate and multiple regression analysis to obtain the final multivariable model able to create the basis for the creation of the DAME score (Table 2).

In particular, the model was derived through a factorial analysis which considered as independent variable the dichotomic (absence/presence) "chest pain". After univariate and multivariate regression analyses, ten variables were considered eligible for the final inclusion into the score: hs-CRP > 3 mg/L, elevation in hs-TnI > 3 ng/L, ESR > 20 mm/h, fever (body temperature > 37°C), chest pain, LVEF < 50% (calculated according to international guidelines [11]), viral prodromes, alterations in electrocardiogram ST-T segment, male gender, increase in white blood cell count.

Although viral prodromes, alterations in electrocardiogram ST-T segment, male gender, and white blood cell count emerged among all the variables considered in the factorial analysis, they were excluded from the final model due to the attributed final null value. Therefore, the six variables composing the final score were: fever, chest pain

Table 1
General characteristics of study population

Total Patients	**104 (100)**
Age (years)	40.2± 16.5
Gender (male)	91 (87)
Emergency Department Clinical Symptoms	
Fever	61 (58)
Viral prodromes	56 (53)
Exertional dyspnea	17 (15)
Acute Heart Failure	5 (4)
Chest pain	90 (86)
Syncope	6 (5)
Tachycardia	22 (20)
Emergency Department Instrumental Findings	
ECG abnormalities	74 (71)
Laboratory findings	
Total Leukocytes (n/mm^3)	10118.8 ±3580.3
Erythrocyte Sedimentation Rate (mm/h)	40.5±27.2
C-reactive protein (mg/L)	69.1 ±72.9
Hemoglobin (g/dL)	13.2±1.7
NT pro-BNP (pg/mL)	4499.7 ±13135.3
Troponins (ng/mL)	9.5 ±15.3
Echocardiographic findings	
Left Ventricle End-diastolic diameter (mm)	50.3±5.1
Left Ventricle End-diastolic volume (mL)	114.6±22.3
Left Ventricle End-systolic volume (mL)	64.8±24.0
Left Ventricle Ejection Fraction (%)	53.6 ±9.1
Left Ventricular Akinesia/hypokinesia	34 (32)
Pericardial effusion	27 (25)
Follow-up (5 years) events	
In-hospital death	1(0.9)
ICD implantation	2(1.9)
LVAD implantation	3(2.8)
Heart transplantation	3(2.8)

Data are represented as number and percentages or mean±standard deviation. ICD: implantable cardioverter defibrillator; LVAD: Left Ventricular Assist Device; NT-proBNP: N-terminal propeptide of the brain natriuretic peptide

Table 2
Multivariable model related to the analysis of the clinical/instrumental characteristics of the patients. Index value of Keiser Meyer Olkin (KMO) equal to 0.570.

	SCORE			
PARAMETER	**1**	**2**	**3**	**4**
Fever	.212	**.706**	.331	-.191
Viral prodromes	.470	.213	.452	-.396
Chest pain	**.618**	-.196	.004	.210
ECG alterations	-.269	-.596	.319	.324
Gender (male)	-.701	.006	.011	-.290
Leucocytes	-.442	.084	.503	-.288
ESR	-.247	**.684**	-.052	.372
CRP	-.273	.379	.387	**.641**
LVEF<50%	**.742**	.165	-.051	.132
Troponins	.237	-.416	**.682**	.095

CRP: C-reactive protein; **ESR**: Erythrocyte Sedimentation Rate; **LVEF**: left ventricle ejection fraction

occurrence at presentation, ESR plasma concentrations, hs-CRP plasma concentrations, hs-troponins serum levels, and LVEF < 50%.

In particular, we observed that score "1" was directly related to LVEF (0.742) and chest pain (0.618); score "2" was correlated to fever (0.706) and ESR (0.684); score "3" was directly related to hs-TnI elevation (0.682); and score "4" was correlated to hs-CRP (0.641).

Table 3 gathers the final determinants of the DAME score for acute evaluation of patients admitted to ED with a possible diagnosis of myocarditis.

All of these variables received a specified score ranging from 0 to 4. A score > 4 was related to 75% probability of myocarditis; a final score ranging between 1 and 4 was related to 57% probability of myocarditis.

Supplemental figure 1 reported the correlation between the days of hospitalization and hemoglobin levels when considering troponins as dependent variable at multivariate regression analysis, showing a good correlation degree ($R^2 = 0.58$). Supplemental figure 2 showed the multivariate regression model correlating changes in ESR and hs-CRP, when assuming troponins serum levels as dependent variable. The supplemental figure 2 also showed a good correlation ($R^2 = 0.73$).

At five-years follow-up, there was only one in-hospital death, while 2 individuals underwent implantable cardioverter defibrillator

Table 3

The *D*iagnosis of *A*cute *M*yocarditis in *E*mergency (DAME) score

PARAMETER	*SCORE*
hs-CRP (mg/L)[a]	4
hs-TnI elevation (ng/L)[b]	3
ESR (mm/h)[c]	2
Fever[d]	2
Chest pain[e]	1
LVEF < 50%[f]	1
Score > 4: 75% risk of myocarditis	
1<Score≤4: 57% risk of myocarditis	

Abbreviations. hs-CRP: high sensitive C-reactive protein; **ESR:** erythrocyte sedimentation rate; **LVEF:** left ventricle ejection fraction; **hs-TnI:** high sensitive troponin I

[a] normal values: < 3 mg/L

[b] normal values: < 3 ng/L

[c] normal values: < 20 mm/h

[d] defined as skin temperature higher than 37◦C within 30 days before the onset of chest pain.

[e] defined as thoracic retrostenal pain which may appear as sharp stab or a discomfort, irradiating to neck, one or both upper arms, or interscapular zone. Its intensity degree may also vary in agreement to patient's positions or in relation to breathe.

[f] defined after standard echocardiographic ultrasound evaluation. Simpons' biplane method should be adopted in order to define LVEF or, at least, 3D chamber evaluation. In case of difficulties in defining endocardial boards, contrast echocardiography can be used.

implantation due to the progression of heart failure. Three patients underwent left ventricle assist device implantation and further three underwent heart transplantation (table 1).

In order to evaluate the performance of the text in a real world setting, we applied the DAME score to a validation cohort of patients admitted to the Cardiology Department of Hospital "F Perinei" Altamura (BA), Italy. We enrolled 289 patients (mean age: 57.85±18.25 years). The clinical characteristics of the validation cohort had been reported in supplemental table 1. The evaluation of definite diagnosis revealed: 27 cases of myocarditis, 144 patients with unstable angina/non ST-elevation myocardial infarction, 36 patients with chronic coronary syndrome, and 82 patients with acute heart failure. After the application of the DAME score, patients with myocarditis revealed a mean score of 10.4 (range: 8-13). The remaining 262 patients with diagnosis other than myocarditis showed a mean DAME score equal to 3.96 (range: 0-11): 149 patients demonstrated a DAME score ≤ 4, while 113 had a DAME score > 4.

The ROC curve demonstrated a sensibility equal to 100%, specificity equal to 85.11% when the cut-off of the DAME score was set > 7, with area under the curve (AUC) 0.958 and $p < 0.001$ (figure 2). PPV and NPV were 40.9% and 100%, respectively, while LR+ and LR- were 6.72 and 0.00, respectively. Logistic regression analysis demonstrated an Odds Ratio (OR) equal to 2.83 (95% CI 1.90 – 4.20, $p < 0.0001$), i.e. each unit increase in DAME score determined a 3-fold increase in myocarditis diagnosis.

5. DISCUSSION

The aim of our study was to provide a score able to guide the decision making process for the diagnosis of myocarditis in patients attending the ED. A multicenter, retrospective analysis on 104 definite cases of myocarditis allowed obtaining the *Diagnosis of Acute Myocarditis in Emergency (DAME)* score which provides a direct kit for reaching the diagnosis of myocarditis with a 75% probability rate.

The need for a score able to predict myocarditis is fundamental for the general management of patients attending the ED. The DAME score would give the opportunity for early suspecting myocarditis within ED, thus preventing delaying in diagnosing or, at least, biases in clinical practice such as the wrong discharge of patients from ED due to underdiagnosed myocarditis. Myocarditis is effectively a rare diagnosis or, at least, a diagnosis derived after excluding major adverse conditions such as acute aortic dissection, pulmonary embolism, acute coronary syndromes, etc. [1, 13]

The DAME score can provide a wide, almost accurate diagnosis of myocarditis even in peripheral health system zones.

The lack of a uniform distribution of certified chest pain units did not allow the use of skills able to early perform a fast probability diagnosis. Varnavas et al. observed that chest pain units can be found within university hospitals or, at least, in tertiary care centers. Nevertheless, rural areas often offered low number of chest pain units. [14]

Indeed, the low incidence in myocarditis diagnosis within ED can be related to the great efforts in identifying myocardial ischemic conditions rather than inflammatory diseases of the myocardium. Roos et al. [15] evaluated 1848 patients attending the ED at Karolinska University Hospital due to chest pain. All of these individuals revealed elevated high sensitive troponins levels but only a reduced number of them were directed to the diagnostic pathway for detecting other cardiac diseases and adequately treated with appropriate cardiovascular drugs. [15]

At the best of our knowledge, there is no score able to guide the myocarditis diagnosis in the ED. Kindermann et al. [16] observed that advanced New York Heart Association (NYHA) functional class, immunohistological findings from endomyocardial biopsies, and lack of treatment with beta-blockers can predict time-to-cardiac death or heart transplantation in patients suffering from acute myocarditis. Nevertheless, these predictors are not useful in acute setting or in addressing diagnosis towards myocarditis. After considering the evaluation of 82 patients with biopsy-proven active myocarditis, Anzini et al. [17] pointed out that the combination of left atrium enlargement, reduced LVEF (<50%) and NYHA class can predict the optimal recovery of the patients suffering from myocarditis at 6 months follow-up (AUC=0.90). [17] Furthermore, it seems that CRP, creatine-kinase plasma levels, the presence of intraventricular conduction alterations, and LVEF could predict the fulminant degeneration of clinical course of myocarditis. [18] NYHA class IV, brain natriuretic peptide (BNP) levels, and LVEF could be considered as independent predictors of mortality in children with myocarditis. [19] Although these are more reliable elements to be observed/measured in acute setting, there is no systematic organization of them into a predictive score.

The DAME score tried to provide a fast, costless, and reproducible tool for better evaluating patients and tried an attempt for a prompt identification of myocarditis. The determinants of the DAME score (i.e. fever, chest pain, ESR, hs-CRP, hs TnI, and LVEF < 50%) had been proven to be highly related to myocarditis diagnosis in previous studies. [17-29]

Studies confirmed that high-sensitive CRP and LVEF <50% are independently associated with the identification of myocarditis. [17-19] Literature provides confounding results about the role of cardiac troponin elevation in diagnosing myocarditis. [20, 21] Bachmaier et al. [22] observed that troponin T can be a more reliable tool than creatine-kinase in myocarditis diagnosis, although they did not used high sensitive assays. The authors pointed out the higher positive predictive value of troponin in the context of myocarditis, although this biomarker showed a low negative predictive value. [22] Nevertheless, most of literature data are about the prognostic role of hs-TnI in myocarditis rather than its exact role in discriminating myocarditis from other causes of troponin elevation. Al-Bitagi et al. [20] observed a direct relationship between myocarditis severity and cardiac troponin levels, while Kyto et al. [21] pointed out the inverse relationship between them. Such differences might be related to the immunological characteristics related to the two isoforms: TnI is able to promote more severe autoimmune inflammatory reactions as compared to troponin T, which lead to fibrosis and heart failure. [23] Therefore, the increase in TnI serum levels can be related to a worsen course of myocardial lesions, leading to negative outcomes for the patients. The DAME score is the first to confer hs-TnI a well-defined diagnostic role in myocarditis.

Inflammatory markers, ESR and hs-CRP, played the most important role in diagnosing myocarditis. The importance of such elements in guiding myocarditis diagnosis is great in the DAME score: 4 and 2 points had been respectively attributed to each one (table 3). The great contribution of inflammatory answer to myocardial damage accounts for the reason why these biomarkers had so great importance within the score. Little data are in literature about the role of ESR and hs-CRP in myocarditis detection. [24-27] CRP is directly related to plasma levels of lactic dehydrogenase and the New York Heart Association functional class in lymphocytic myocarditis. [24] Campana et al. revealed a direct relationship between ESR and myocarditis: only patients with biopsy-proven myocarditis showed an increase in ESR among 28 patients admitted to ED with suspected myocarditis. [28] Indeed, hs-CRP is a well-established prognostic biomarker in cardiovascular diseases. Ciliberti et al. [29] demonstrated a 47% increase in risk for the composite endpoint of cardiovascular death, acute coronary syndrome, heart failure, stroke in patients with myocardial infarction and non-obstructed coronary arteries (MINOCA), although patients with myocarditis were excluded from their study.

The role of echocardiography should also be emphasized when suspecting myocarditis. The DAME score attribute 1 point to LVEF < 50% (table 3). The score pointed out the need for the use of echocardiography in the acute setting of the ED. It is already established the fundamental role of bedside echocardiography [30, 31] as well as its reproducibility as compared to standard echocardiographic approaches. [32] Nevertheless, the ultrasound evaluation is often underused within ED. This may lead to reducing the possibility of final diagnosis and, therefore,

giving the exact treatment of patients.

The validation cohort of the DAME score provided useful insights in daily application of this tool in clinical practice.

The high sensibility (100%), specificity (85.11%), and negative predictive value (100%) of DAME score > 7 in detecting patients with myocarditis is a great goal for this predictive model.

The impressive AUC (0.958, 95% CI 0.928-0.978, p<0.001) of the ROC curve from the validation cohort promotes the adoption of DAME score in clinical practice for the sake of patients' health. Such results were prompted from LR: the LR+ equal to 6.72 effectively means that patients with a DAME > 7 have a 6.72x more likely probability to be true positive; the LR- value equal to 0.00 means that patients with DAME score > 7 are 100% less likely to be false negative.

The DAME score is a clinical score: the application in daily clinical practice, since ED setting, can really improve the diagnostic challenges in myocarditis. As each unit increase in DAME score is able to improve myocarditis prediction by about 3-fold, the higher the number of signs/symptoms/laboratory biomarkers, the better the identification of disease and the reduction in misleading diagnosis.

In the end, we created a possible flow diagram for guiding decision making and application of DAME score in ED (figure 1): after the clinical examination of patients admitted to ED for chest pain, instrumental and laboratory evaluations should be performed. Echocardiography will be performed in order to evaluate signs for acute coronary syndrome (unstable angina, non-ST elevation-acute coronary artery diseases, ST elevation myocardial infarction) or other acute "thoracic" syndrome (acute aortic diseases, pneumothorax, pulmonary artery embolism, etc). In case of presence of signs indicating acute coronary syndromes or other acute "thoracic" syndrome, patients will undergo coronary angiography or computer tomography evaluations. Otherwise, the application of the DAME score for final detection of a possible myocarditis will be performed.

6. LIMITATIONS

None of the patients, both in derivative and validation cohorts, underwent myocardial biopsies as the risks of the procedure outweighed the benefits from a definite diagnosis. A further limitation may derive

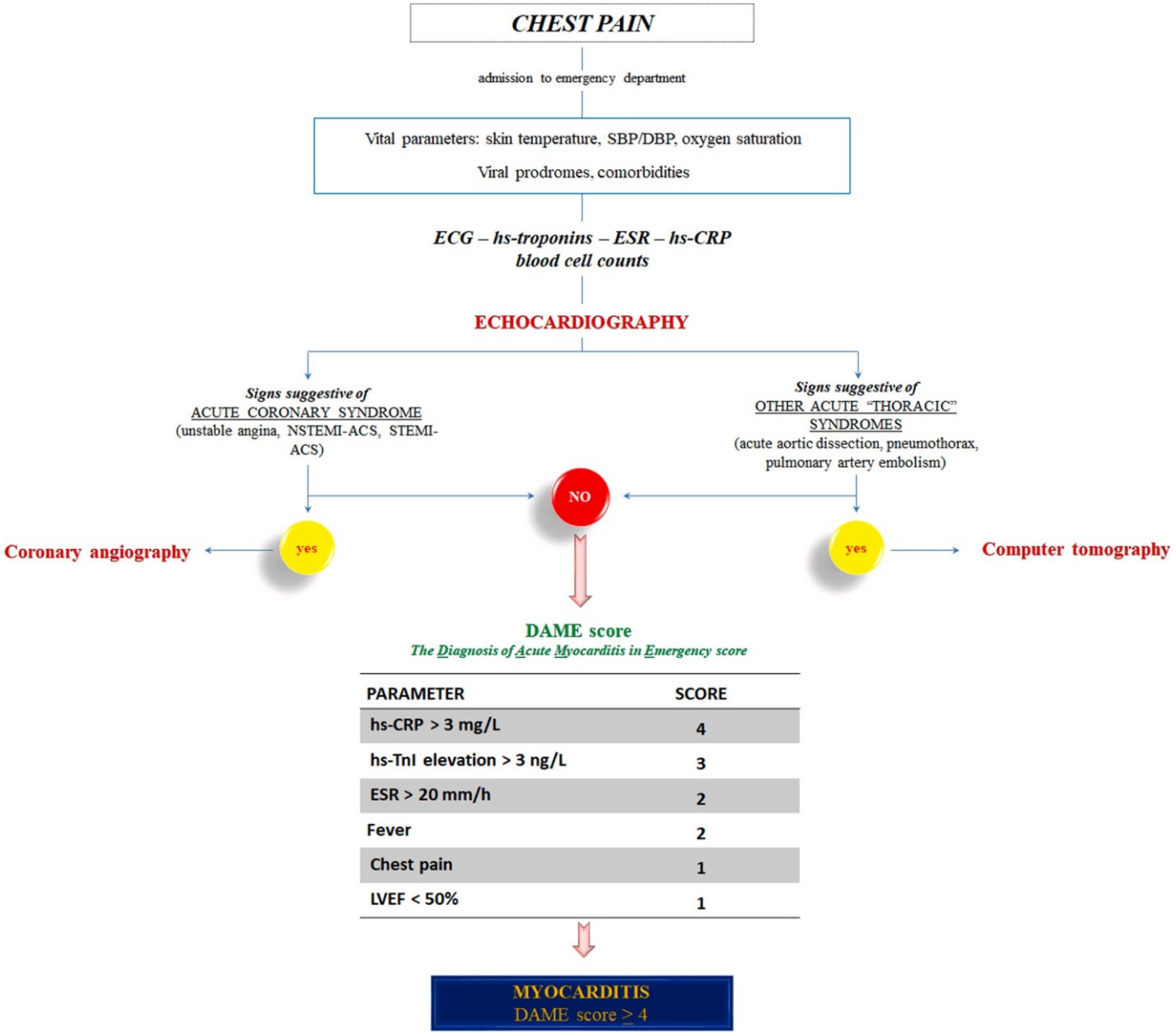
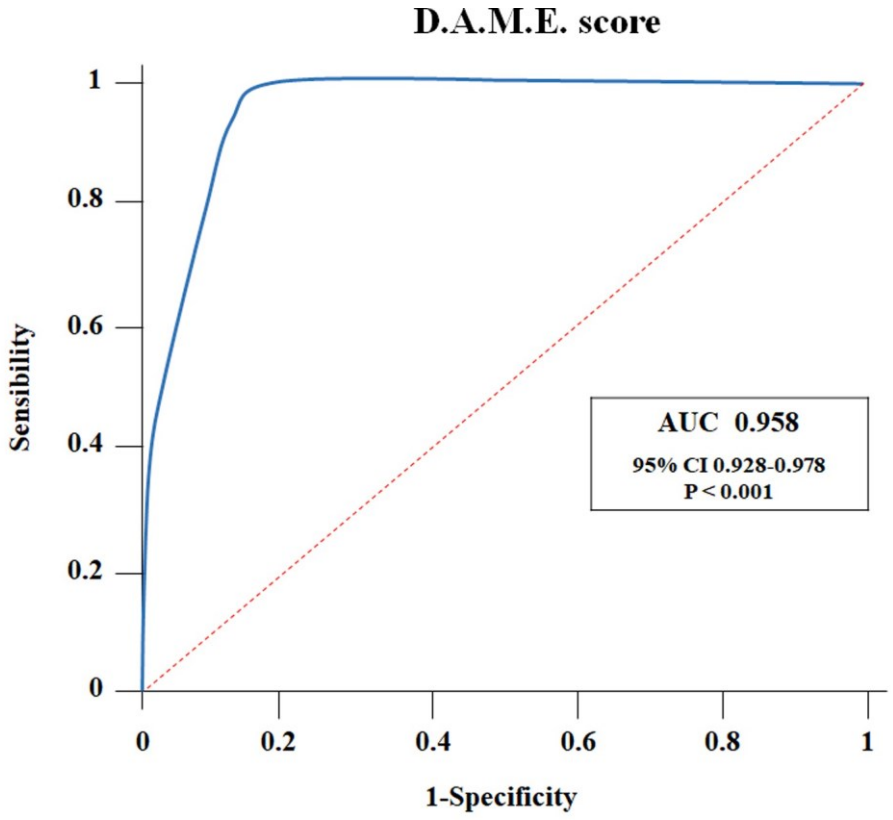


Figure 1. Proposed diagnostic algorithm for detection of myocarditis within the Emergency Department setting.



Score	Sensibiltiy	95% CI	Specificity	95% CI	LR+	LR-	PPV	95% CI	NPV	95% CI
>7	100	87.2-100	85.11	80.2-89.2	6.72	0.00	40.9	34.1-48.0	100	/

Figure 2. Receiver operating characteristic (ROC) curves for detection of myocarditis considering a DAME score > 7. Sensibility, specificity, positive (PPV) and negative (NPV) predictive values are reported.

from the laboratory assays. For example, conventional CRP assays are more available than hs-CRP, especially in low-volume hospital. Therefore, this can influence the performance of the score in case of unavailable hs-CRP assays. Same considerations are in relation to hs-TnI. Nevertheless, the widespread of hs-TnI assays is covering all the laboratories of the Italian hospital, thus reducing the confusion deriving from previous conventional TnI assays.

7. CONCLUSIONS

The diagnosis of myocarditis is challenging. The DAME score seems to provide a useful tool able to predict the risk of myocarditis in patients admitted to emergency department for chest pain.

Conflicts of Interest and Source of Funding

None declared.

Sources of Funding, disclosures, conflict of interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.01.011.

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