ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Role of HEART score in prediction of coronary artery disease and major adverse cardiac events in patients presenting with chest pain

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SUMMARY

Introduction Chest pain (CP) diagnostics accuracy remains debatable for both general practitioners (GP) or emergency department (ED) physicians for patients in HEART score (HS) low- and intermediate-risk groups which prompted us to review our electronic database for all patients admitted via our center's ED during 2014 to 2020 for CP and suspect acute coronary syndrome.

Methods Patients were divided in function of low- or intermediate-risk HS and assessed during a three month follow up for angiogram results, major adverse cardiac events (MACE), lab results and echo parameters.

Results Of 585 patients included, low-risk HS group (21,4%, 36% were women) had significant coronary disease on angiogram in 68%, while for intermediate-risk HS group (78.6%, with 32.6% women) it was for 18.4% of patients (p < 0,0005). Area under the ROC curve of HS in detecting patients with ischemic heart disease as a cause of CP was 0.771 (95% CI: 0.772–0.820) with best cut-off point HS was calculated at 3.5. Sensitivity and specificity were 89.2% and 57.6% respectively. Adjusting for sex, lab results and HS, AUROC curve of this model was 0.828 (95% CI: 0.786–0.869; p < 0,0005) with cut-off of 77.95. Sensitivity and specificity were 84.9% and 68% respectively. In the three-month follow-up post-discharge, there was a significant difference in MACE between groups (low- *vs*. intermediate-risk HS was 3.4 *vs*. 16.7% p < 0.05).

Conclusion HS for our CP patients admitted via our ED by GP and ED physicians' referral, provides a quick and reliable prediction of ischemic heart disease and MACE.

Keywords: Chest pain; HEART score; MACE; general practitioner

INTRODUCTION

Between 20% and 40% of general population experience some kind of chest pain (CP) during life [1] and the first to see the patient is the general practitioner (GP), while many of these patients are ultimately sent to the hospital for further diagnostics or intervention. In the United States, 2–5% of patients with an acute coronary syndrome (ACS) are misdiagnosed and inappropriately discharged, even from emergency department (ED) [2]. Therefore, some clinicians refer patients to additional diagnostic procedures aiming to establish the cause of CP, even in the case of a low-risk patients, leading to increased resource utilization [3, 4]. A small number of studies evaluated the accuracy of initial diagnosis in patients with CP in primary health care, especially concerning ischemic heart disease (IHD), with no data about final treatment outcomes in patients with initial misdiagnosis [5]. In the great majority of patients with CP, GPs considered coronary artery disease (CAD) unlikely diagnosis. This initial assessment agrees with the findings of various epidemiological studies in the field of

primary care, which describe IHD prevalence of 8% to 15% [6, 7]. Set against this is IHD prevalence of over 50% in patients who present to a hospital ED with CP [8, 9]. The first opinion of the GP regarding presence of IHD showed at best moderate diagnostic accuracy, with a sensitivity of 68% [10]. One of the most challenging tasks GPs face is to adequately triage patients with undifferentiated CP. Often, it is not an easy task because CP evaluation is frequently subjective and different between GP, other clinicians and cardiologists. To accurately manage the cause of CP, GP or ED clinician should use some of the easily accessible and applicable tools for identification of low-risk CP patients, suitable for discharge with deferred additional diagnostics. Some of these scores are Thrombolysis in Myocardial Infarction (TIMI) score; The Platelet Glycoprotein IIb/IIIb in Unstable Angina–Receptor Suppression Using Integrilin Therapy score; Global Registry of Acute Coronary Events score; Fast Revascularization in InStability in Coronary Disease score and History, ECG, Age, Risk factors, T-troponin (HEART) score. Six, Backus and Kelder developed the HEART score (HS)

in 2008, as a rapid risk stratification tool for patients with CP to help identification of low-risk patients, suitable for earlier ED discharge [11]. While the latest AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guidelines for the Evaluation and Diagnosis of Chest Pain recommend the TIMI score for the initial evaluation of a patient with CP [1], it is not the best tool for identification of low-risk CP patients [12, 13]. For this subset of patients, HS achieved better results, as well as in patients with a high risk of major adverse cardiac events (MACE). The negative predictive value of HS is superior compared to other scoring systems. This study aimed to estimate sensitivity and specificity of the HS in our patient population for detection of positive coronary angiography finding and its correlation with MACE in low-risk patients' subset presenting with CP.

METHODS

In this retrospective follow-up study approved by the local Ethics Committee (No 3674/10 of December 11, 2019), we analyzed patients with CP and suspected ACS who presented to Institute of Cardiovascular Diseases of Vojvodina's ED, in the period between 2014 and 2020.

Inclusion criteria were as follows: age over 21 years; CP; percutaneous coronary angiography or CT coronary angiography upon admission; biochemical analysis of high sensitivity Troponin (hsT) and calculated HS from 0 to 6. Exclusion criteria were *de novo* ECG changes (ST elevation or denivelation of more than 1 mm); hypotension and calculated HS 7 to 10.

HS is consistently validated rapid use risk stratification tool for patients with CP in the ED, considering History, ECG, Age, Risk factors and Troponin. In each category are three possible scores: 0.1 and 2. Final HS is sum of five single category scores. In this study we analyzed value of low-risk (0–3) and intermediate-risk (4–6) HS in prediction of IHD and MACE. Patients with CP were chosen randomly to achieve a minimum of 120 patients' group with a HS 0–3 (HS 0–3) and minimum of 120 patients in the group of HS ranging 4–6 (HS 4–6). All of these patients were admitted to the hospital and underwent coronary angiography. Degree of coronary artery stenosis greater than 50 % was defined as significant. The follow-up period for both groups of patients was three months post-discharge during which we assessed difference between groups' survival and incidence of MACE defined as new ACS, stroke, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and IHD-related death. In addition to validation of HS in prediction of IHD and MACE, we analyzed predictive value of creatine kinase MB and fasting glucose levels; ejection fraction and left ventricle volumes and diameters. The data were provided from hospital database and by calling patients and their families in case of their further medical treatment in other hospital. Statistical analysis included descriptive statistics such as arithmetic mean, standard deviation, median, quartile, frequency and percentages. Comparison of mean values of variables of two groups of patients was realized by t – test
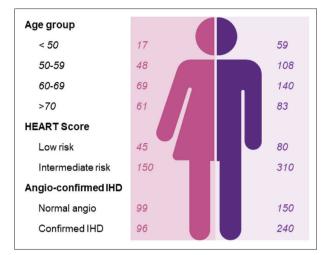

Figure 1. Sex differences in description of HEART score and angiography results
IHD – ischemic heart disease

and Mann–Whitney test. Categorical variables were compared with the χ^2 test or Fisher exact test. Univariate and multivariate binary logistic regression we used to determine influence of variables on final outcomes. Predictive values of variables were estimated with the ROC curve. Two-sided P values of less than .05 were considered to be significant for all analyses. All statistical analyses were performed with SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 585 patients with CP enrolled in the FU study, 125 patients (21.4%) were in low-risk HS group (HS 0–3) and 460 patients (78.6%) in the intermediate-risk HS group (HS 4–6). Sex distribution was similar for both groups (36% in HS 0–3 *vs*. 33.6% in HS 4–6) and together with sex-specific description for HS and angiography are presented in Figure 1. Number of patients with hypertension was significantly higher in HS group 4–6 (HS 4–6 74% *vs*. HS 0–3 63%; p < 0.05). Previous myocardial infarction (MI), PCI and CABG were predominant in intermediate-risk HS group (previous MI/PCI/CABG HS 4–6 15.7/15.7/5.4 % *vs*. HS 0–3 1.6/2.4/0 %; p < 0.05). The distribution of other risk factors in the two groups is shown in Table 1. Echocardiography data analysis showed a significant difference between groups in left ventricular ejection fraction, diameters and volumes – both systolic and diastolic (Table 2.). Lab results of interest showed significantly higher blood levels of creatine kinase MB, urea and creatinine in intermediate-risk HS group (Table 3.). Invasive coronary imaging was performed in higher percentage in intermediate-risk HS group (HS 4–6 83.7% *vs*. HS 0–3 64.8%; p < 0.0005), while others were offered non-invasive, CT coronary angiography. There was significant difference in coronary angiography findings between groups. In intermediate-risk HS group, significant coronary disease (stenosis > 50%) was present in 68% of patients *vs*. low-risk HS group where IHD was confirmed in 18.4% of patients (p < 0.0005). Patients with

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Table 1. Distribution of different variables in HEART score groups

Variables	HS 0–3	HS 4–6	p
Sex Men Women	 80 (64%) 45 (36%)	 310 (67.4%) 150 (32.6%)	0.544
Hypertension	79 (63.2%)	341 (74.1%)	0.022
Smoking	43 (34.4%)	167 (36.3%)	0.773
Hyperlipoproteinemia	37 (29.6%)	170 (37%)	0.156
Diabetes mellitus	23 (18.4%)	74 (16.1%)	0.631
Previous myocardial infarction	2 (1.6%)	72 (15.7%)	< 0.0005
Previous PCI	3 (2.4%)	72 (15.7%)	< 0.0005
Previous CABG	0	25 (5.4%)	0.004
Previous stroke	2 (1.6%)	14 (3%)	0.542
Troponin	11 (8.8%)	188 (40.8%)	< 0.0005
Mitral valve insufficiency	6 (5%)	47 (10.8%)	p = 0.012
Aortic valve insufficiency	8 (6.6 %)	25 (5.7%)	p = 0.745

HS – HEART score; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting

Table 2. Echocardiographic data analysis in HEART score groups

Variables	HS groups	Percentiles			p
		25th	50 (median)	75th	
EF	HS 0–3	55	60	61	< 0.0005
	HS 4–6	47	55	60	
IVSd	HS 0–3	1.10	1.20	1.30	0.113
	HS 4–6	1.10	1.20	1.30	
PLWd	HS 0–3	1.05	1.20	1.30	0.192
	HS 4–6	1.10	1.20	1.30	
LVIDs	HS 0–3	2.65	3	3.40	0.005
	HS 4–6	2.80	3.20	3.70	
LVIDd	HS 0–3	4.50	4.75	5.10	0.001
	HS 4–6	4.60	4.90	5.30	
EDVLV	HS 0–3	72.50	91	115	0.002
	HS 4–6	80	100	121	
ESVLV	HS 0–3	29.50	38.50	52	< 0.0005
	HS 4–6	34	46	61	

HS – HEART score; EF – ejection fraction; IVSd – interventricular septal diameter; PLWd – posterior wall thickness at end-diastole; LVIDs – left ventricular internal dimension at end-systole; LVIDd – left ventricular internal dimension at end-diastole; EDVLV – end-diastolic volume of the left ventricle; ESVLV – end-systolic volume of left ventricle

Table 3. Biochemical data analysis in HEART score groups

Variables	HS groups	Percentiles			p
		25th	50 (median)	75th	
CK-MB	HS 0–3	16	20	27.50	0.012
	HS 4–6	18	25	40	
FG	HS 0–3	5.45	6.15	7.25	0.524
	HS 4–6	5.70	6.40	8	
s-Urea	HS 0–3	4.30	5.40	7.40	0.041
	HS 4–6	5.10	6.30	8.60	
s-Creatinine	HS 0–3	74	86	98	< 0.0005
	HS 4–6	81	98	114.50	
CRP	HS 0–3	2.30	4.20	10	0.224
	HS 4–6	2.85	5.70	13.50	
LDH	HS 0–3	165	194	236	0.220
	HS 4–6	170.50	200	245.50	

CK-MB – creatine kinase MB; FG – plasma fibrinogen; CRP – C-reactive protein; LDH – lactate dehydrogenase
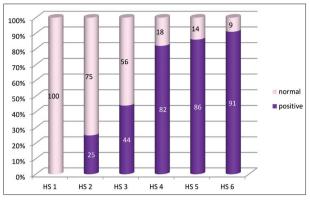

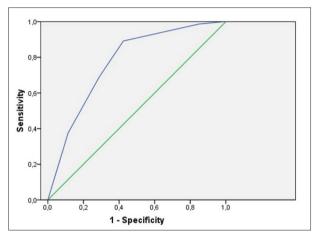**Figure 2.** Influence of HEART score value on positive coronary angiography finding

Figure 3. ROC curve of HEART score in detecting patients with ischemic heart disease

confirmed IHD on coronary angiography, had two- and three-vessel CAD. There was no difference between HS groups in distribution of patients according to severity of the CAD. In both HS groups, approximately two thirds of IHD-confirmed patients had significant stenosis of two and more vessels (HS 0–3 65.2% *vs*. HS 4–6 70%; p = 0.642). Patients with HS 1 were free of CAD. Results for other HS subgroups are shown in Figure 2. The area under the ROC curve of HS in detecting patients with IHD as a cause of CP was 0.771 (95% CI:0.772–0.820). The best cut-off point for the HS in this regard was calculated at 3.5. The sensitivity and specificity were 89.2% and 57.6% respectively (Figure 3.).

Binary logistic regression was used to show influence of different factors of confirmed CAD. The odds ratio (OR) for HS groups was 11.653 (7.094–19.143). Intermediate-risk HS group had 11.6-time higher risk of having IHD compared to low-risk HS group. Creatine kinase MB and glucose blood level odds ratios were 1.022 (1.006–1.038) and 1.131 (1.019–1.256) respectively. Results are shown in Table 4.

Integrating sex, creatine kinase MB, glucose blood level and HS, the AUROC curve of this model was 0.828 (95% CI:0.786–0.869; p < 0.0005). The cut-off point was 77.95. The sensitivity and specificity were 84.9% and 68% respectively (Figure 4.).

Table 4. Results of univariate and multivariate binary logistic regression for different variables

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Sex	0.60 (0.403–0.895)	0.012	0.587 (0.357–0.966)	0.036
History	1.376 (1.079–1.754)	0.010	/	ns
ECG	2.615 (1.819–3.761)	< 0.0005	/	ns
Troponin	3.607 (2.371–5.486)	< 0.0005	/	ns
EF	0.952 (0.929–0.976)	< 0.0005	/	ns
LVIDd	1.414 (1.052–1.899)	0.021	/	ns
LVIDs	1.449 (1.029–2.041)	0.034	/	ns
EDVLV	1.010 (1.003–1.016)	0.003	/	ns
ESVLV	1.015 (1.005–1.024)	0.002	/	ns
CK-MB	1.026 (1.012–1.040)	< 0.0005	1.022 (1.006–1.038)	0.006
FG	1.137 (1.031–1.254)	0.010	1.131 (1.019–1.256)	0.021
HEART score	11.190 (7.099–17.637)	< 0.0005	11.653 (7.094–19.143)	< 0.0005

ECG – electrocardiogram; EF – ejection fraction; LVIDd – left ventricular internal dimension at end-diastole; LVIDs – left ventricular internal dimension at end-systole; EDVLV – end-diastolic volume of the left ventricle; ESVLV – end-systolic volume of left ventricle; CK-MB – creatine kinase MB; FG – plasma fibrinogen
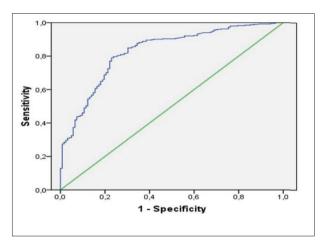

Figure 4. ROC curve of integrated sex, creatine kinase MB, glucose blood level and HEART score in detecting patients with ischemic heart disease
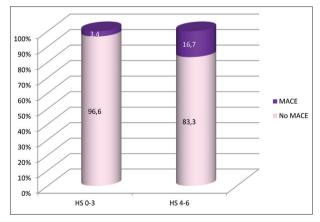

Figure 5. Incidence of MACE in HEART score groups

In three-months follow-up period post-discharge, there was significant difference in MACE between groups (HS 0–3 3.4% *vs*. HS 4–6 16.7% p < 0.05) (Figure 5.).

DISCUSSION

HS is a risk stratification score used for patients with CP with suspected non-ST elevation ACS. Simple to use and widely validated as a risk stratification tool, its accuracy is still somewhat questioned for predictive power in detecting of significant CAD.

Our study included patients who were admitted to the cardiology department as a result of a physician's clinical decision. The present study showed 21.4% of patients, with CP who met inclusion criteria, classified as low-risk HS patients. This result is not consistent with the study by van Meerten et al. [14] where low-risk HSs were calculated in 36.4% of the patients, while Soares et al. reported low-risk HS present in 33% of patients by research generated score and 25% by ED clinician score [15]. In a meta-analysis of 25 studies published from 2010 to 2017, with a total of 25,266 patients, 39.3% were deemed to have low-risk HS [16]. A lower percentage of low-risk HS patients in our study should be explained by the study population selected only from patients admitted according to inclusion criteria.

Hypertension, ACS with/without previous PCI and CABG, as a part of HEART scoring criteria, were present in expectedly higher percentage in the intermediate-risk HS group. There was a significant difference between groups in ejection fraction; systolic and diastolic diameters and volume of left ventricle with lower ejection fraction and larger diameters and volumes of the left ventricle in intermediate-risk HS group as a result of impaired left ventricular function caused by IHD which is present in higher percentage in this group of patients – all to be expected with a pre-existing burden of disease.

In our study, we determined the HS to be a diagnostic predictor of severe coronary artery stenosis (minimum one coronary artery stenosis >50%) with positive findings in 18.4% of patients in low-risk group and 68% of patients in the intermediate-risk group. The area under the ROC curve of HS in detecting patients with IHD as a cause of CP was 0.771 (95% CI: 0.772–0.820). The best cut-off point for the score in this regard was calculated in 3.5. The sensitivity and specificity were 89.2% and 57.6% respectively. In a paper published by Han et al. [17], where significant coronary artery stenosis was defined more than 70%, they found that the diagnostic accuracy of the HS is better for significant coronary artery stenosis than for ACS. They demonstrated that HS can be considered a useful tool for determining early invasive measures based on the objective results of coronary visualization. Backus et al. [18] lowered the value of the risk factor element and weighted history and troponin elements. There was some improvement in calibration and discrimination, but its clinical usefulness was relatively small. We had a different approach in modifying the HS by integrating sex, creatine kinase MB, glucose blood level and HS. Compared with the sensitivity

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and specificity of the HS, our modification had nearly the same sensitivity, but improved specificity.

The three-months follow-up post-discharge, showed a significant difference in MACE between groups (low-HS 3.4% *vs*. intermediate-HS 4–6 16.7% p < 0.05). Reported incidence of MACE in the low-risk HS group by van Meerten et al. [14] was in 1.7% of patients which should be basis to skip redundant testing and move to quicker discharge. Oh and coworkers found a 0.6% risk of MACE in low-risk CP patients from North Carolina [19]. The higher incidence of MACE in our study population should be explained by the possible presence of other risk factors that are not included in the HS.

Implementation of HS in the routine practice of GP or ED physicians, should avoid further unnecessary observation and noninvasive and invasive cardiac testing. Admission of low-risk patients for further examination is time-consuming, expensive, and in some cases harmful. A widespread invasive cardiac testing may lead to patient harm. One example is radiation exposure [20] since a dose of 10 mSv may increase the risk of fatal cancer, which can be a public health concern in the reality of the increased number of diagnostic tests including radiation exposure [21]. Also, introduction of HEART scoring cut costs over $4.5 million annually and invasive imaging in a similar sized sample as ours [4].

There is evidence that HS compares favorably with other CP decision scores. TIMI score, when applied to patients with undifferentiated CP has not performed as well, with a poor prognostic ability [22].

Although a detailed sex-specific analysis was not the scope of this publication, our low-risk HS and intermediate-risk HS groups encompassed 36% *vs*. 32.6% women respectively, in a representative sample for the region where awareness of heart disease in women is very physician-dependent [23]. Also, additional imaging needed for patients who were considered lacking angiographically significant stenoses, was not routinely provided in the investigated period irrelevant of sex, although long-term clinical benefits are well known, especially for women [24, 25, 26].

Preciado et al. [27], in a far larger sample size, but time-frame-wise appropriate with ours, noted women were hospitalized or received stress testing less frequently than men for low-HS (18.8% *vs*. 22.8%; OR 0.79; 95% CI 0.73–0.84) and intermediate-HS (46.7% *vs*. 49.7%; OR 0.88; 95% CI 0.83 to 0.95), although their outcomes were better, finding it still inappropriate. Still, per latest data women and patients of color remain those less likely to receive HS risk stratification when presenting with undifferentiated CP [28]. However, although – per latest United Nations High Commissioner for Refugees and UNICEF reports – since 2015, more than 1.5 million refugees and migrants have passed through Serbia, while during 2020, the number of refugees and migrants present in Serbia at any given time was around 7,000 and accommodated in reception, transit and asylum centers around 6,000 [29] which is the upper cut off for country's hosting limit [30], our reported sample was native Caucasian population not out of discrimination, but management system of refugee populations is handled differently.

Study limitations

Limitations of our study include single-center, retrospective design and a small sample size with limited projection to the whole population that is mainly Caucasian White. The HS was not applied to all CP patients, but rather those with met inclusion criteria including percutaneous coronary angiography or CT coronary angiography upon admission to our tertiary level University hospital.

CONCLUSION

Use of HS scoring system for patients with CP who presented to our center's ED by GP referral of our own ED physicians' one provided a quick and reliable prediction of IHD as a cause of CP and MACE. Appropriate assessment of borderline patients with traditionally called "atypical" we nowadays term "sex specific" symptoms, should be improved by application of HS in routine practice by both GP and ED physicians aiming to stratify better populations deemed of intermediate or low-risk, in particular women whose awareness for CAD needs to be improved.

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HEART скор у предикцији коронарне болести и значајних нежељених кардиоваскуларних догађаја код болесника са болом у грудима

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САЖЕТАК

Увод Прецизност дијагностике бола у грудима остаје најдискутабилнија за лекаре како опште праксе, тако и ургентних центара за болеснике ниског и средњег *HEART* скора (ХС), што нас је навело на ретроспективну анализу наших електронских историја болести у циљу процене свих хоспитализованих због бола у грудима са сумњом на акутни коронарни синдром преко нашег Ургентног центра у периоду 2014–2020.

Методе Болесници су подељени у групе ниског и средњег ХС и у тромесечном праћењу процењивани су резултати коронарографије, великих кардиолошких нежељених догађаја (*MACE*), лабораторијски резултати и ехокардиографски параметри.

Резултати Од 585 укључених болесника, у групи ХС ниског ризика (21,4%, 36% жена) ангиографски значајну коронарну болест је имало 68%, док у групи ХС средњег ризика (78,6%, 32,6% жена) то је случај са 18,4% болесника (*p* < 0,0005). Регија под *ROC* кривом ХС за детекцију болесника са коронарном болешћу као узроком бола у грудима била је 0,771 (95% *CI*: 0,772–0,820) са *cut off*-ом ХС 3,5. Сензитивност и специфичност су биле 89,2%, тј. 57,6%. Интеграцијом пола, лабораторијских параметара и ХС, *AUROC* крива за овај модел је била 0,828 (95% *CI*: 0,786–0,869; *p* < 0,0005) са *cut off*-ом од 77,95. Сензитивност и специфичност су биле 84,9%, тј. 68%. Током тромесечног праћења по отпусту, забележена је значајна разлика у *MACE* између две групе (ХС ниског спрам средњег ризика била је 3,4 према 16,7% *p* < 0,05).

Закључак ХС за наше болеснике са болом у грудима примљене кроз наш Ургентни центар по упуту како лекара опште праксе, тако и лекара Ургентног центра, представља брз и поуздан предиктивни скор за коронарну болест и *MACE*.

Кључне речи: бол у грудима; *HEART* скор; *MACE*; лекар опште праксе