European Journal of Internal Medicine 64 (2019) 57–62

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Biomarker assessment for early infarct size estimation in ST-elevation myocardial infarction

Christina Tiller[a], Martin Reindl[a], Magdalena Holzknecht[a], Maximilian Klapfer[a], Alexander Beck[a], Benjamin Henninger[b], Agnes Mayr[b], Gert Klug[a], Sebastian Johannes Reinstadler[a], Bernhard Metzler[a,*]

[a] University Clinic of Internal Medicine III, Cardiology and Angiology, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria
[b] University Clinic of Radiology, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria

ARTICLE INFO

Keywords:
ST-segment elevation myocardial infarction
High-sensitivity cardiac troponin T
Infarct size
Cardiac magnetic resonance imaging
Risk stratification

ABSTRACT

Background: High-sensitivity cardiac troponin T (hs-cTnT) represents the biomarker of choice for infarct size (IS) estimation in patients with acute ST-elevation myocardial infarction (STEMI). However, admission values of hs-cTnT are only weakly associated with IS. The aim of this study was to investigate the incremental value of different biomarkers measured on admission for IS estimation in STEMI patients.

Methods: In this prospective observational study, we included 161 consecutive STEMI patients treated with primary percutaneous coronary intervention (pPCI). The following biomarkers were assessed on admission: hs-cTnT, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and neutrophil/lymphocyte ratio (NLR). IS was determined by cardiac magnetic resonance (CMR) imaging 3 (Interquartile range [IQR] 2 to 4) days after the index event.

Results: Patients with large IS (> 19% of left ventricular myocardium) showed significantly higher levels of admission hs-cTnT (399.6 vs. 53.4 ng/L, $p < .001$), NT-pro-BNP (140 vs. 86 ng/L, $p = .008$) and NLR (6.4 vs. 4.1, $p < .001$). The combination of hs-cTnT, NT-pro-BNP and NLR on admission resulted in a significantly higher area under the curve (0.78; 95% CI 0.704 to 0.838, ($p = .01$)) for the prediction of large IS than admission hs-cTnT alone (0.69; 95% CI 0.619 to 0.767).

Conclusions: In STEMI patients undergoing pPCI, a comprehensive biomarker approach on admission including hs-cTnT, NT-pro-BNP and NLR was significantly better for immediate infarct severity estimation as compared to hs-cTnT alone.

1. Introduction

Infarct size (IS) is of major prognostic relevance in patients suffering from ST-elevation myocardial infarction (STEMI) [1]. Cardiac magnetic resonance (CMR) represents the in vivo gold standard for IS evaluation and several previous studies could affirm the strong and, as compared to established clinical risk models, incremental value of CMR-determined IS for the prediction of adverse clinical outcome after STEMI [1,2].

Over the last years, high-sensitivity cardiac troponin T (hs-cTnT) has emerged as biomarker of choice for myocardial damage assessment in the setting of acute STEMI [3]. Particularly, the peak value of hs-cTnT has proven to be a robust indicator of IS and is therefore widely used in clinical routine [4–6]. However, due to the delayed release kinetics, the clinical value of hs-cTnT is noticeably limited at the early stage of acute STEMI [4]. Therefore, more accurate ways of early IS estimation are needed. Above and beyond biomarkers of myocardial necrosis per se, markers of myocardial wall stress (natriuretic peptides) as well as markers of inflammation are correlated with myocardial injury and previous data indicate that even early measurements of such biomarkers can be useful in terms of IS prediction [7–10]. However, a potential incremental value of admission levels of natriuretic peptides or inflammatory markers over hs-cTnT for IS estimation has never been studied in STEMI patients so far.

We therefore sought to investigate (a) the value of hs-cTnT, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and inflammatory markers for the prediction of CMR determined IS and (b) the potential benefit of a multimarker approach over hs-cTnT only assessment in patients with STEMI undergoing primary percutaneous coronary intervention (pPCI).

* Corresponding author.
E-mail address: Bernhard.Metzler@tirol-kliniken.at (B. Metzler).

https://doi.org/10.1016/j.ejim.2019.03.001
Received 17 December 2018; Received in revised form 3 February 2019; Accepted 5 March 2019
Available online 14 March 2019

2. Methods

2.1. Study design and clinical assessments

In this prospective observational study, we included 161 patients with first acute STEMI admitted to the coronary care unit (CCU) of Innsbruck University Hospital. The following inclusion criteria were exerted: first STEMI defined in accordance with the redefined ESC/ACC committee criteria [11], revascularization by pPCI within 24 h after symptom onset, an estimated glomerular filtration rate > 30 mL/min/1.73m^2 and Killip class < 3 at time of CMR. Exclusion criteria were age < 18 years, any history of a previous myocardial infarction or coronary intervention and any contraindication to CMR (pacemaker, orbital foreign body, any aneurysm clips, claustrophobia, known or suggested contrast agent allergy to gadolinium).

All biomarker concentrations were assessed via peripheral venipuncture on hospital admission. Concentrations of hs-cTnT were analysed by using an enzyme immunoassay (hs-cTnT; E170, Roche Diagostics®, Vienna, Austria) with the analytical limit of detection and the 99th percentile upper reference limit of 5 ng/l and 14 ng/l, respectively [6]. For high sensitivity C-reactive protein (hs-CRP) the c702 module of cobas® 8000 (Roche Diagnostics®) was applied and for white blood cell count (WBCc) measurements as well as their subtypes Sysmex XE-5000 [12]. NT-pro-BNP levels were determined by a commercially available assay (E170 instrument proBNP II assay, Roche Diagnostics®, Vienna, Austria) [13].

For risk stratification, we developed a biomarker score for the prediction of large IS after STEMI, including hs-cTnT, NT-pro-BNP and NLR. For each of the three biomarkers 1 point was assigned if the concentrations were elevated above the best cut-off resulting in a score range from 0 to 3 points. The best cut-off values for the biomarkers were determined via Youden Index [14]. Higher score points were associated with a significant (p = .01) and stepwise increase in large IS rates (0 points: 23%, 1 point: 31%, 2 points: 58%, 3 points: 76%, Fig. 2).

All participants gave their written informed consent before inclusion in the present study. The study was approved by the local research ethics committee and conducted in accordance with the Declaration of Helsinki.

2.2. Cardiac magnetic resonance imaging

CMR examinations were performed 3 (Interquartile range [IQR 2 to 4]) days after infarction. All CMR scans were carried out on a 1.5 Tesla Magnetom AVANTO-scanner (Siemens, Erlangen, Germany). The detailed imaging protocol of our research group was published previously [15]. Left ventricular (LV) volumes and function were assessed on short-axis (10 to 12 slices) cine images using breath-hold, retrospective ECG-triggered trueFISP bright-blood sequences. Papillary muscles were assigned to the LV volume [2]. For post-processing, standard software (ARGUS, Siemens, Erlangen, Germany) was applied.

Late gadolinium enhancement (LGE) images were taken 15 min after intravenous administration of 0.2 mmol/kg of Gd-DO3A-butriol (Gadovist®, Bayer Vital, Leverkusen, Germany) at 2 ml/s, followed by 20 ml of saline flush, administered using an automatic injector (Spectris Injection System, Medrad, Pittsburgh, USA). An ECG-triggered phase-sensitive inversion recovery sequence with full coverage of left ventricle short-axis slices was applied. Each slice of the LGE extent was quantified by using a PACS workstation (IMPAX®, Agfa HealthCare, Bonn, Germany). We characterized "hyperenhancement" as +5 standard deviations (SD) above the signal intensity of vital myocardium in the opposite myocardial segment of the LV [16,17]. IS was shown as percentage of LV myocardial mass. According to the prognostic data published by Eitel et al. IS > 19% was defined as large IS [18]. All CMR images were evaluated by experienced observers, blinded to clinical events and angiographic results.

2.3. Statistical analysis

Statistical analysis was performed with SPSS Statistics 24.0 (IBM, Armonk, NY, USA), MedCalc Version 15.8 (Ostend, Belgium) and R 3.3.0 (The R Foundation, Austria). Continuous variables were presented as median with corresponding IQR. Differences in two groups of continuous variables were compared using the Mann–Whitney U test. Categorical variables were defined as absolute numbers and percentages. Spearman test was used to calculate the correlation of continuous variables and Chi-square test was used to compare categorical variables. Receiver-operating characteristic (ROC) curve analysis was used to quantify the value for IS prediction. Area under the curve (AUC) differences were tested according to the method described by DeLong [19] and Hanley & McNeil [20]. According to the definition of Rice and Harris [21], the AUC values were interpreted using the following categories: negligible (≤0.55), small (0.56–0.63), moderate (0.64–0.70) and strong (≥0.71). To further analyse significant predictors of IS, univariable and multivariable logistic regression analyses were calculated. According to the results of multivariable regressions analysis, we developed a risk score, incorporating all variables with a p-value < .05 (1 point for each variable if biomarker concentration > best cut-off value). For all statistical tests, a p-value < .05 was considered significant.

3. Results

3.1. Study population and baseline characteristics

We included 161 consecutive STEMI patients with a median ischemia time of 175 (IQR 120 to 257) minutes. The median age of the overall cohort was 56 (49–67) years. A detailed overview on baseline characteristics is listed in Table 1.

3.2. Relation between biomarkers and infarct size

Table 1 also provides all parameters divided into two groups according to the severity of myocardial damage (IS < 19%, n = 80; IS > 19%, n = 81). Hs-cTnT, NT-pro-BNP and NLR showed significant correlation with IS (r = 0.4222, p < .001 vs. r = 0.210 p = .008 vs. r = 0.360, p < .001). Patients with large IS represented significantly higher hs-cTnT (p < .001) and higher NT-pro-BNP (p = .008) values on admission. Absolute neutrophils (p = .007), absolute lymphocytes (p = .024) and the neutrophil/lymphocyte Ratio (NLR) (p < .001) illustrated significant associations with IS. The relations between large IS and high-sensitivity C-reactive protein (hs-CRP) (p = .085) or WBCc (p > .05) were not significant. Creatine kinase also indicated an association with IS but on multivariable analysis there was no independent prediction for large IS.

Furthermore, the presence of pre-interventional TIMI flow 0 showed significant (p < .001) association with large IS as well as the extent of ST-segment elevation (p = .002) and the heart rate (p = .012) (Table 2).

3.3. Predictive values of biomarkers

A baseline multivariable model was created including hs-cTnT, total ischemia time, killip class, heart rate, systolic blood pressure and the extent of ST-segment elevation. Adding post interventional TIMI flow to the baseline model did not add any significance. Adding NT-pro-BNP and NLR did add significant value to the baseline model and therefore, on multivariable logistic regression analysis hs-cTnT, NT-pro-BNP as well as NLR independently predicted large IS (Table 3). The AUC of cTnT, NT-pro-BNP and NLR were 0.69 (95% confidence interval (CI) 0.619 to 0.767), 0.61 (95% CI 0.531 to 0.686) and 0.66 (95% CI 0.576 to 0.728) respectively. The optimal cut-off value for hs-cTnT was 169.8 ng/L, for NT-pro-BNP 98.0 ng/L and for NLR 5.1. The

Table 1
Patient characteristics.

	Total population (n = 161)	IS < 19% (n = 80)	IS > 19% (n = 81)	p-value
Age, years	56 [49–67]	56 [49–68]	57 [49–67]	0.875
Female, n (%)	28 (17)	16 (20)	12 (15)	0.385
Body mass index, kg/m^2	26.3 [24.4–29.1]	26.3 [24.3–28.6]	26.6 [24.4–29.3]	0.332
Hypertension, n (%)	63 (39)	32 (40)	31 (38)	0.822
Systolic blood pressure, mmHg	129 [110–150]	128 [111–150]	130 [107–144]	0.819
Diastolic blood pressure, mmHg	80 [69–98]	80 [70–99]	80 [68–98]	0.684
Heart rate, min	71 [63–83]	69 [61–80]	78 [64–90]	**0.012**
Current smoker, n (%)	101 (62.7)	52 (65)	49 (61)	0.554
Hyperlipidaemia, n (%)	80 (50)	45 (56)	35 (43)	0.098
Diabetes mellitus, n (%)	15 (9)	6 (8)	9 (11)	0.431
Total ischemia time, min	175 (120–257)	150 (105–248)	189 (128–270)	**0.021**
Pre-interventional TIMI flow 0, n (%)	101 (63)	39 (46)	62 (82)	< **0.001**
Post-interventional TIMI flow 3, n (%)	140 (87)	77 (91)	63 (83)	0.148
Extent ST-segment elevation, mV	0.30 [0.20–0.45]	0.25 [0.15–0.40]	0.35 [0.25–0.50]	**0.002**
Hs-cTnT, ng/L	114 [25–1186]	53 [16–260]	400 [39–4110]	< **0.001**
Creatine kinase, U/l	245 [124–955]	162 [100–306]	611 [166–2432]	< **0.001**
Hs-CRP, mg/dL	0.2 [0.1–0.5]	0.2 [0.1–0.4]	0.3 [0.1–0.5]	0.085
WBCc, G/L	12.3 [9.7–15.0]	11.4 [8.5–15.3]	12.6 [10.8–14.8]	0.157
Absolute neutrophils, G/L	9.9 [7.1–12.5]	8.6 [5.3–11.8]	10.7 [8.3–12.6]	**0.007**
Eosinophils, %	0.6 [0.2–1.4]	0.7 [0.3–1.7]	0.4 [0.1–1.0]	0.075
Basophils, %	0.2 [0.1–0.3]	0.2 [0.1–0.3]	0.2 [0.1–0.2]	0.156
Monocytes, %	4.8 [3.7–6.4]	5.0 [3.6–7.0]	4.7 [3.8–6.2]	0.267
Absolute lymphocytes, G/L	1.8 [1.3–2.4]	1.8 [1.4–2.6]	1.7 [1.2–2.3]	**0.024**
NLR Ratio	5.4 [3.2–8.0]	4.1 [2.4–6.7]	6.4 [4.1–8.6]	< **0.001**
Fibrinogen, mg/dL	287 [240–339]	272 [239–339]	294 [246–345]	0.396
NT-pro-BNP, ng/L	118 [50–277]	86 [50–237]	140 [69–579]	**0.008**

IS = Infarct size; hs-cTnT = high-sensitivity cardiac Troponin T; hs-CRP = high-sensitivity C-reactive protein; WBCc = white blood cell count; NLR = neutrophil to lymphocyte ratio; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide. p-values < 0.05 were highlighted in bold.

Table 2
Univariable analysis for the prediction of infarct size.

	Univariable analysis	
	OR (95% CI)	p-value
Hs-cTnT	2.19 (1.55 to 3.09)	< **0.001**
NLR Ratio	7.29 (2.29 to 23.22)	**0.001**
NT-pro-BNP	2.79 (1.44 to 5.42)	**0.002**
Total ischemia time	3.55 (1.00 to 12.60)	0.050
Systolic blood pressure	0.83 (0.03 to 25.70)	0.917
Heart rate	54.79 (1.85 to 1620.72)	**0.021**
Killip class	1.68 (0.94 to 3.00)	0.082
Post-interventional TIMI flow 0/1/2/3	0.31 (0.20 to 0.50)	< **0.001**
Extent ST-segment elevation	8.33 (2.05 to 33.76)	**0.003**

Hs-cTnT = high-sensitivity cardiac Troponin T; NLR = neutrophil to lymphocyte ratio; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; OR = Odds ratio; CI = Confidence interval. p-values < 0.05 were highlighted in bold.

combination of all three biomarkers on admission did reveal a higher AUC for the prediction of large IS (AUC = 0.78, 95% CI 0.704 to 0.838, p = .01; Fig. 1) than hs-cTnT alone. Also in comparison with routinely available parameters including admission hs-cTnT, total ischemia time, killip class, heart rate, systolic blood pressure, extent of ST-segment elevation as well as the post interventional TIMI flow, adding NLR and NT-pro-BNP yielded in a higher AUC (0.775 vs. 0.820; p = .049).

In an explorative analysis, we divided the ischemia time according to the median (175 min) to evaluate a potential impact of ischemia time on the predictive value of biomarker assessment. In the group of patients with an ischemia time < 175 min (n = 81), the combination of hs-cTnT, NLR and NT-pro-BNP revealed a higher AUC for the prediction of large IS (AUC = 0.70, 95% CI 0.584 to 0.819, p = .002) than hs-cTnT alone (AUC = 0.57, 95% CI 0.431 to 0.704, p = .306). In the group with an ischemia time > 175 min (n = 80), combined biomarkers also showed a higher AUC for IS prediction (AUC = 0.83, 95% CI 0.738 to 0.919, p < .001) than hs-cTnT alone (AUC = 0.78, 95% CI 0.685 to 0.882, p < .001).

Concerning biomarker risk score, higher score points were related

Table 3
Multivariable analysis for the prediction of infarct size.

	Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Hs-cTnT	2.31 (1.50 to 3.57)	< **0.001**	1.92 (1.28 to 2.89)	**0.002**
NLR Ratio			7.60 (1.99 to 29.01)	**0.003**
NT-pro-BNP			2.41 (1.08 to 5.39)	**0.033**
Total ischemia time	2.76 (0.55 to 13.76)	0.215	1.59 (0.27 to 9.27)	0.608
Systolic blood pressure	1.92 (0.02 to 182.19)	0.779	0.51 (0.001 to 43.36)	0.764
Heart rate	4.22 (0.08 to 237.69)	0.484	6.78 (0.13 to 345.59)	0.340
Killip class	2.15 (1.01 to 4.56)	**0.046**	1.47 (0.75 to 2.90)	0.264
Post-interventional TIMI flow 0/1/2/3			0.847 (0.29 to 2.43)	0.757
Extent ST-segment elevation	13.56 (2.77 to 66.38)	**0.001**	20.53 (4.22 to 99.87)	< **0.001**

Hs-cTnT = high-sensitivity cardiac Troponin T; NLR = neutrophil to lymphocyte ratio; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; OR = Odds ratio; CI = Confidence interval. p-values < 0.05 were highlighted in bold.

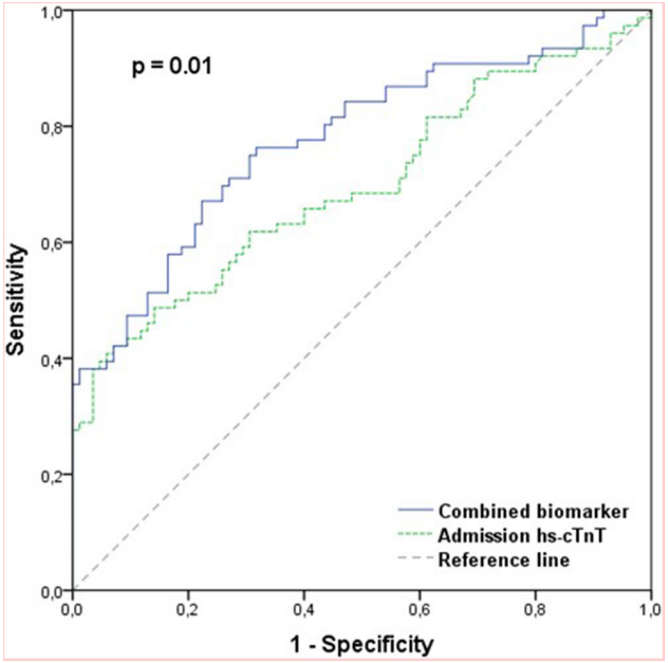

Fig. 1. ROC curves for the prediction of large IS (> 19% LVMM) after STEMI. Abbreviations: ROC = Receiver operating characteristic, IS = infarct size, LVMM = left ventricular mass, STEMI = ST-elevation myocardial infarction, hs-cTnT = high-sensitivity cardiac troponin T, NT-pro-BNP = N-terminal pro-B-type natriuretic peptide, NLR = neutrophil to lymphocyte ratio.

with a stepwise increase in rates of large IS: 0 points: 23%, 1 point: 31%, 2 points: 58%, 3 points: 76% (p-value < .001, Fig. 2).

4. Discussion

This is the first comprehensive study investigating the value of combined admission biomarker assessment for IS estimation in STEMI patients treated by pPCI. The major findings are as follows: (1) hs-cTnT, NT-pro-BNP and NLR emerged as independent predictors of IS as determined by CMR imaging and (2) the combination of these three biomarkers yielded a significant better IS estimation as compared to hs-cTnT alone.

4.1. Predictive value of biomarkers

Hs-cTnT was shown to be closely related with IS after STEMI [22]. Especially peak values correlated well with IS [5]. However, admission values only poorly correlate with IS [23]. Chia et al. showed no association of hs-cTnT on admission and IS estimation whereas Nyguen et al. described weak but significant relation between admission hs-cTnT and IS [23,24]. This very weak association might be explained by the delayed release kinetics of hs-cTnT [25]. In line with this study, we also found significant association of hs-cTnT with IS on admission. However, the predictive value was only moderate. Therefore, more comprehensive ways of early IS estimation are needed.

Before the era of hs-cTnT, creatine kinase has been shown to correlate well with IS. However, due to the distribution of CK in different organs the values vary and based on the release kinetics of CK in the context of myocardial necrosis the admission values are not satisfying. In the present study, admission CK values were associated with IS but did not show an independent prediction for large IS.

In the acute setting after STEMI, NT-pro-BNP is a quantitative marker of hemodynamic cardiac stress and is being released due to mechanical stretch of the ventricular myocardium [26]. Several studies showed a relation between NT-pro-BNP and IS after STEMI [27,28]. However, data concerning relationship between NT-pro-BNP on admission and IS are very limited in the present literature. Scintigraphic data reported significant relations between NT-pro-BNP levels, measured on admission, and the extent of myocardial damage [29]. Our CMR investigation could affirm the usefulness of admission NT-pro-BNP for IS estimation. Importantly, the association between admission NT-pro-BNP and IS could be demonstrated to remain significant even after adjustment for hs-cTnT, indicating that NT-pro-BNP provides predictive information incrementally to hs-cTnT. Indeed, c-statistics confirmed

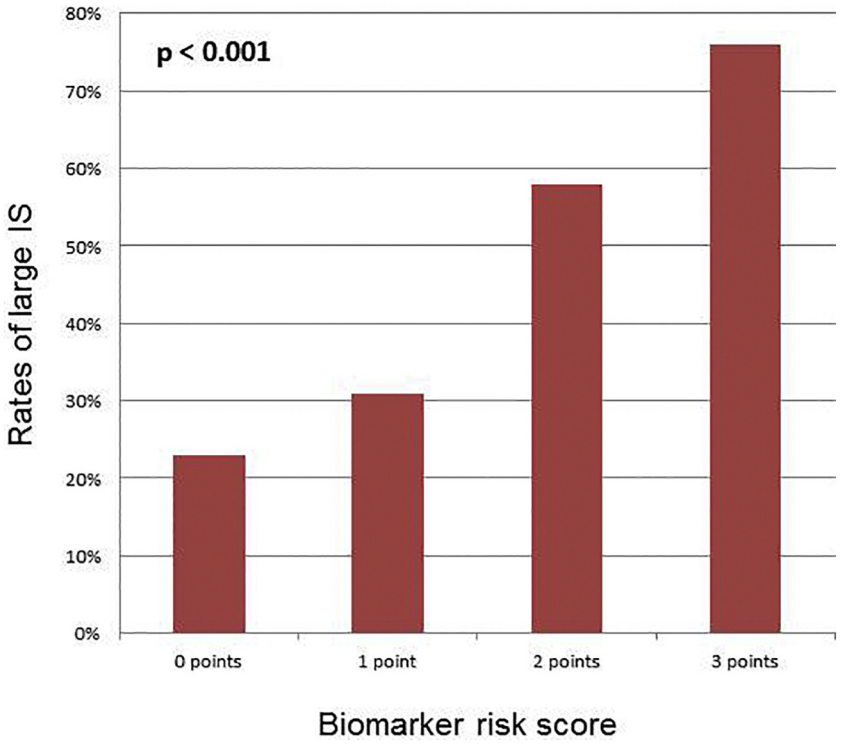

Fig. 2. The relationship between the clinical risk score (x-axis) and the prediction of IS (%, y-axis). Three biomarkers were included into the scoring system: hs-cTnT > 169.8 ng/L, NT-pro-BNP > 98 ng/L and NLR Ratio > 5.1 (1 scoring point for each parameter); score range from 0 to 3 points. Abbreviations: IS = infarct size, hs-cTnT = high-sensitivity cardiac troponin T, NT-pro-BNP = N-terminal pro-B-type natriuretic peptide, NLR = neutrophil to lymphocyte ratio.

that the additional determination of NT-pro-BNP is useful in terms of IS estimation improvement.

Inflammatory processes play a pivotal role in the pathogenesis and also in the acute setting of myocardial infarction. Due to myocardial ischaemia, the immune system is activated, locally as well as systemically with a release of different cells and biomarkers detectable in peripheral blood [8]. CRP is one of the most important acute-phase reactant, induced by tissue injury and mediated by hepatic production [30]. Previous studies could find a relation between hs-CRP measured at 48 h after infarction and IS [31], whereas admission levels of hs-CRP did not correlate with IS [10], probably due to the delayed CRP release [32]. In line with those previous data, no significant association between admission hs-CRP and IS was found in the present analysis. Therefore, hs-CRP seems to be an insufficient marker for early IS prediction. Beyond hs-CRP, necrosis of cardiomyocytes triggers a complex inflammatory cascade with a recruitment of pro-inflammatory leukocytes [33]. Evidence exist that there is a relationship between WBCc and IS, however the association was described only moderate [34,35]. In the present study WBCc on admission tended to be related with large IS. Therefore, WBCc is not accurate enough in the early phase of STEMI for IS estimation. More recently, studies notably focused on leukocyte subtypes, especially the NLR. The NLR combines the neutrophils, as reflectors for innate immune response, and the lymphocytes, representing the adaptive immune response, into one variable and showed more prognostic relevance concerning clinical outcome and mortality following STEMI than the absolute WBCc [36]. In particular, neutrophils seem to play an early role in the ischemic myocardium with a rapid occurrence of neutrophilia within the first hour after AMI [37], while a drop in lymphocyte count is probably owing to heart protection from an overshoot of neutrophils [38]. Due to this premature neutrophil release, the NLR could be more relevant in early IS estimation than the WBCc. In contrast to overall WBCc, this present study showed significant correlation between both neutrophils and lymphocytes and the extent of myocardial damage. In line with our findings, Chia et al. found a significant association of NLR and IS on admission [39]. From all inflammatory parameters, NLR revealed as the best marker as well as an independent biomarker for IS estimation. Therefore, NLR should be considered to be utilized in daily clinical routine.

In an explorative analysis, we evaluated the potential impact of ischemia time on the predictive value of biomarker assessment. The AUC for the detection of large IS by combined biomarkers (hs-cTnT, NLR and NT-pro-BNP) was weaker in the subgroup with shorter delays. However, the predictive value of combined biomarkers remained significant compared to hs-cTnT alone. Further prospective studies are necessary to address this important issue in detail.

4.2. Clinical relevance

Due to the high prognostic value of IS [40], early detection of the extent of myocardial damage is of crucial significance for post-STEMI risk stratification. Currently, risk scores for the prediction of IS after STEMI are limited. Here we propose a novel biomarker score on admission, including three, easy to obtain biomarkers (hs-cTnT, NT-pro-BNP and NLR) with a positive predictive value of up to over 75% (Fig. 2). This score may be used as a robust prognostic indicator for the severity of myocardial damage in patients presenting with STEMI, irrespective of angiographic findings and interventions.

4.3. Limitations

This study has several limitations. First, only stable STEMI patients with Killip < 3 were included in order to perform a high quality CMR scan; therefore, the findings of the present study may not be generalizable to critically ill patients or patients with early complications. Nevertheless, data from large studies confirmed nearly 90% of patients with STEMI present with Killip < 3 [41]. Secondly, further studies are necessary to demonstrate if our results are applicable to patients with non-STEMI or patients with unsuccessful PCI. Reperfusion success with pPCI influences the extent of myocardial damage [42]. Since the majority of our patients were successfully treated with pPCI, concordant with current literature [43], the present data cannot be generated to patients with non-successful pPCI. Therefore, further studies are needed to evaluate the proposed score in patients with unsuccessful pPCI. Thirdly, emerging biomarkers that have been shown to be associated with IS after STEMI, such as copeptin and fetuin-A have not been analysed [44,45]. However, these biomarkers are not available in clinical routine so far. Finally, the present study is a single center study and should therefore be validated in an external cohort to prove the results independently.

5. Conclusion

A multimarker approach including hs-cTnT, NT-pro-BNP and NLR provided higher value for IS estimation than hs-cTnT alone. Consequently, a multimarker approach provides an easy clinical tool for early IS prediction and therefore risk stratification of STEMI patients.

Funding sources

This study was funded by grants from the ‘Austrian Society of Cardiology’, the “Tiroler Wissenschaftsfonds” and by an intramural funding program of the Medical University Innsbruck for young scientists MUI-START, Project 2015-06-013.

Conflict of interest

The Authors declare that there is no conflict of interest.

References

[1] Reinstadler SJ, Thiele H, Eitel I. Risk stratification by cardiac magnetic resonance imaging after ST-elevation myocardial infarction. Curr Opin Cardiol 2015;30:681–9. Review 2015/09/24 https://doi.org/10.1097/HCO.0000000000000227.

[2] Klug G, Metzler B. Assessing myocardial recovery following ST-segment elevation myocardial infarction: short- and long-term perspectives using cardiovascular magnetic resonance. Expert Rev Cardiovasc Ther 2013;11:203–19. Review 2013/02/15 https://doi.org/10.1586/erc.12.173.

[3] Mair J. High-sensitivity cardiac troponins in everyday clinical practice. World J Cardiol 2014;6:175–82. Review 2014/04/29 https://doi.org/10.4330/wjc.v6.i4.175.

[4] Laugaudin G, Kuster N, Petiton A, et al. Kinetics of high-sensitivity cardiac troponin T and I differ in patients with ST-segment elevation myocardial infarction treated by primary coronary intervention. Eur Heart J Acute Cardiovasc Care 2016;5:354–63. Observational Study 2015/05/07 https://doi.org/10.1177/2048872615585518.

[5] Boden H, Ahmed TA, Velders MA, et al. Peak and fixed-time high-sensitive troponin for prediction of infarct size, impaired left ventricular function, and adverse outcomes in patients with first ST-segment elevation myocardial infarction receiving percutaneous coronary intervention. Am J Cardiol 2013;111:1387–93. Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't 2013/03/08 https://doi.org/10.1016/j.amjcard.2013.01.284.

[6] Reinstadler SJ, Feistritzer HJ, Klug G, et al. High-sensitivity troponin T for prediction of left ventricular function and infarct size one year following ST-elevation myocardial infarction. Int J Cardiol 2016;202:188–93. Research Support, Non-U.S. Gov't 2015/09/24 https://doi.org/10.1016/j.ijcard.2015.09.001.

[7] Kleczynski P, Legutko J, Rakowski T, et al. Predictive utility of NT-pro BNP for infarct size and left ventricle function after acute myocardial infarction in long-term follow-up. Dis Markers 2013;34:199–204. 2013/01/22 https://doi.org/10.3233/DMA-120955.

[8] Ruparelia N, Chai JT, Fisher EA, et al. Inflammatory processes in cardiovascular disease: a route to targeted therapies. Nat Rev Cardiol 2017;14:314. 2017/03/17 https://doi.org/10.1038/nrcardio.2017.33.

[9] Reinstadler SJ, Feistritzer HJ, Reindl M, et al. Utility of NT-proBNP in predicting infarct scar and left ventricular dysfunction at a chronic stage after myocardial infarction. Eur J Intern Med 2016;29:e16–8. Letter Research Support, Non-U.S. Gov't 2016/01/19 https://doi.org/10.1016/j.ejim.2015.12.018.

[10] Reindl M, Reinstadler SJ, Feistritzer HJ, et al. Relation of inflammatory markers with myocardial and microvascular injury in patients with reperfused ST-elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2017;6:640–9. 2016/07/22 https://doi.org/10.1177/2048872616661691.

[11] Myocardial infarction redefined–a consensus document of The Joint European

Society of Cardiology/American College of Cardiology Committee for the re-definition of myocardial infarction. Eur Heart J 2000;21:1502–13. 2000/09/07 https://doi.org/10.1053/euhj.2000.2305.
[12] Reinstadler SJ, Klug G, Feistritzer HJ, et al. Relation of plasma adiponectin levels and aortic stiffness after acute ST-segment elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2014;3:10–7. Research Support, Non-U.S. Gov't 2013/12/18 https://doi.org/10.1177/2048872613516015.
[13] Reinstadler SJ, Feistritzer HJ, Klug G, et al. Biomarkers of hemodynamic stress and aortic stiffness after STEMI: a cross-sectional analysis. Dis Markers 2015;2015:717032. Research Support, Non-U.S. Gov't 2015/05/12 https://doi.org/10.1155/2015/717032.
[14] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5. [1950/01/01].
[15] Klug G, Trieb T, Schocke M, et al. Quantification of regional functional improvement of infarcted myocardium after primary PTCA by contrast-enhanced magnetic resonance imaging. J Magn Resonan Imag JMRI 2009;29:298–304. 2009/01/24 https://doi.org/10.1002/jmri.21498.
[16] Bondarenko O, Beek AM, Hofman MB, et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson 2005;7:481–5. [Research Support, Non-U.S. Gov't 2005/05/11].
[17] Reindl M, Reinstadler SJ, Feistritzer HJ, et al. Fibroblast growth factor 23 as novel biomarker for early risk stratification after ST-elevation myocardial infarction. Heart 2017;103:856–62. Observational Study Research Support, Non-U.S. Gov't 2016/12/17 https://doi.org/10.1136/heartjnl-2016-310520.
[18] Eitel I, de Waha S, Wohrle J, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1217–26. Multicenter Study 2014/09/23 https://doi.org/10.1016/j.jacc.2014.06.1194.
[19] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45. [Comparative Study Research Support, U.S. Gov't, Non-P.H.S. 1988/09/01].
[20] Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839–43. 1983/09/01 https://doi.org/10.1148/radiology.148.3.6878708.
[21] Rice ME, Harris GT. Comparing effect sizes in follow-up studies: ROC area, Cohen's d, and r. Law Hum Behav 2005;29:615–20. 2005/10/29 https://doi.org/10.1007/s10979-005-6832-7.
[22] Mayr A, Mair J, Klug G, et al. Cardiac troponin T and creatine kinase predict mid-term infarct size and left ventricular function after acute myocardial infarction: a cardiac MR study. J Magn Reson Imag JMRI 2011;33:847–54. 2011/03/31 https://doi.org/10.1002/jmri.22491.
[23] Chia S, Senatore F, Raffel OC, et al. Utility of cardiac biomarkers in predicting infarct size, left ventricular function, and clinical outcome after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2008;1:415–23. Clinical Trial, Phase II Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't 2009/05/26 https://doi.org/10.1016/j.jcin.2008.04.010.
[24] Nguyen TL, Phan JA, Hee L, et al. High-sensitivity troponin T predicts infarct scar characteristics and adverse left ventricular function by cardiac magnetic resonance imaging early after reperfused acute myocardial infarction. Am Heart J 2015;170:715–25. e712. 2015/09/21 https://doi.org/10.1016/j.ahj.2015.06.022.
[25] Giannitsis E, Becker M, Kurz K, et al. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. Clin Chem 2010;56:642–50. Research Support, Non-U.S. Gov't 2010/02/20 https://doi.org/10.1373/clinchem.2009.134460.
[26] Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8. Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S. Review 1998/07/31 https://doi.org/10.1056/NEJM199807303390507.
[27] Bruder O, Jensen C, Jochims M, et al. Relation of B-type natriuretic peptide (BNP) and infarct size as assessed by contrast-enhanced MRI. Int J Cardiol 2010;144:53–8. Comparative Study 2009/05/05 https://doi.org/10.1016/j.ijcard.2009.03.139.
[28] Mayr A, Mair J, Schocke M, et al. Predictive value of NT-pro BNP after acute myocardial infarction: relation with acute and chronic infarct size and myocardial function. Int J Cardiol 2011;147:118–23. Comparative Study 2009/11/10 https://doi.org/10.1016/j.ijcard.2009.09.537.
[29] Ndrepepa G, Braun S, Mehilli J, et al. N-terminal pro-brain natriuretic peptide on admission in patients with acute myocardial infarction and correlation with scintigraphic infarct size, efficacy of reperfusion, and prognosis. Am J Cardiol 2006;97:1151–6. 2006/04/18 https://doi.org/10.1016/j.amjcard.2005.11.029.
[30] Kavsak PA, AR MacRae, Yerna MJ, et al. Analytic and clinical utility of a next-generation, highly sensitive cardiac troponin I assay for early detection of myocardial injury. Clin Chem 2009;55:573–7. Research Support, Non-U.S. Gov't 2009/01/27 https://doi.org/10.1373/clinchem.2008.116020.
[31] Orn S, Manhenke C, Ueland T, et al. C-reactive protein, infarct size, microvascular obstruction, and left-ventricular remodelling following acute myocardial infarction. Eur Heart J 2009;30:1180–6. Research Support, Non-U.S. Gov't 2009/03/21 https://doi.org/10.1093/eurheartj/ehp070.
[32] Sanchez PL, Rodriguez MV, Villacorta E, et al. Kinetics of C-reactive protein release in different forms of acute coronary syndrome. Revista espanola de cardiologia 2006;59:441–7. [2006/06/06].
[33] Frangogiannis NG. Inflammation in cardiac injury, repair and regeneration. Curr Opin Cardiol 2015;30:240–5. Research Support, N.I.H., Extramural Review 2015/03/26 https://doi.org/10.1097/HCO.0000000000000158.
[34] Chung S, Song YB, Hahn JY, et al. Impact of white blood cell count on myocardial salvage, infarct size, and clinical outcomes in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a magnetic resonance imaging study. Int J Cardiovasc Imaging 2014;30:129–36. Observational Study 2013/10/10 https://doi.org/10.1007/s10554-013-0303-x.
[35] Husser O, Bodi V, Sanchis J, et al. White blood cell subtypes after STEMI: temporal evolution, association with cardiovascular magnetic resonance–derived infarct size and impact on outcome. Inflammation 2011;34:73–84. Research Support, Non-U.S. Gov't 2010/04/27 https://doi.org/10.1007/s10753-010-9209-0.
[36] Sawant AC, Adhikari P, Narra SR, et al. Neutrophil to lymphocyte ratio predicts short- and long-term mortality following revascularization therapy for ST elevation myocardial infarction. Cardiol J 2014;21:500–8. 2013/10/22 https://doi.org/10.5603/CJ.a2013.0148.
[37] Liebetrau C, Hoffmann J, Dorr O, et al. Release kinetics of inflammatory biomarkers in a clinical model of acute myocardial infarction. Circ Res 2015;116:867–75. Research Support, Non-U.S. Gov't 2014/12/18 https://doi.org/10.1161/CIRCRESAHA.116.304653.
[38] Bodi V, Sanchis J, Nunez J, et al. Uncontrolled immune response in acute myocardial infarction: unraveling the thread. Am Heart J 2008;156:1065–73. Research Support, Non-U.S. Gov't Review 2008/11/27 https://doi.org/10.1016/j.ahj.2008.07.008.
[39] Chia S, Nagurney JT, Brown DF, et al. Association of leukocyte and neutrophil counts with infarct size, left ventricular function and outcomes after percutaneous coronary intervention for ST-elevation myocardial infarction. Am J Cardiol 2009;103:333–7. Randomized Controlled Trial Research Support, Non-U.S. Gov't 2009/01/27 https://doi.org/10.1016/j.amjcard.2008.09.085.
[40] Miller TD, Christian TF, Hopfenspirger MR, et al. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. Circulation 1995;92:334–41. Clinical Trial Research Support, Non-U.S. Gov't 1995/08/01.
[41] Johnston N, Bornefalk-Hermansson A, Schenck-Gustafsson K, et al. Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada? Eur Heart J Acute Cardiovasc Care 2013;2:350–8. Multicenter Study Research Support, Non-U.S. Gov't 2013/12/18 https://doi.org/10.1177/2048872613496940.
[42] Joost A, Stiermaier T, Eitel C, et al. Impact of initial culprit vessel flow on infarct size, microvascular obstruction, and myocardial salvage in acute reperfused ST-elevation myocardial infarction. Am J Cardiol 2016;118:1316–22. 2016/10/25 https://doi.org/10.1016/j.amjcard.2016.07.056.
[43] Brener SJ, Moliterno DJ, Aylward PE, et al. Reperfusion after primary angioplasty for ST-elevation myocardial infarction: predictors of success and relationship to clinical outcomes in the APEX-AMI angiographic study. Eur Heart J 2008;29:1127–35. 2008/04/01 https://doi.org/10.1093/eurheartj/ehn125.
[44] Reinstadler SJ, Klug G, Feistritzer HJ, et al. Copeptin testing in acute myocardial infarction: ready for routine use? Dis Markers 2015;2015:614145. Review 2015/05/12 https://doi.org/10.1155/2015/614145.
[45] Feistritzer HJ, Klug G, Reinstadler SJ, et al. Fetuin-A is related to infarct size, left ventricular function and remodelling after acute STEMI. Open Heart 2015;2:e000244. 2015/07/22 https://doi.org/10.1136/openhrt-2015-000244.