

Multi-biomarker approach for predicting cardiac magnetic resonance parameters at 30 days after ST-segment elevation myocardial infarction

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ABSTRACT

Background: Established biomarkers are used for risk stratification after STEMI, but their relationship with cardiac magnetic resonance (CMR)-derived infarct characteristics at 30 days remains incompletely understood. Because 30-day CMR reflects an intermediate post-infarction stage between acute myocardial injury and the later chronic infarct state, we evaluated whether baseline high-sensitivity troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), cellular communication network factor 1 (CCN1), and proprotein convertase subtilisin/kexin type 9 (PCSK9) are associated with 30-day CMR parameters.

Methods: In this pre-specified CLEVER-ACS substudy, associations between baseline biomarkers and 30-day CMR parameters were assessed using Spearman correlation. Receiver operating characteristic (ROC) analysis with area under the curve (AUC) was performed for associations after median dichotomization. Exploratory analyses assessed associations with relative CMR changes.

Results: 56 STEMI patients were analyzed. hsTnT and NT-proBNP showed the strongest association pattern across functional, structural, volumetric, and microvascular 30-day CMR parameters. CCN1 was associated only with left ventricular ejection fraction (LVEF), and PCSK9 showed no significant associations. hsTnT and NT-proBNP showed relevant discriminatory performance for parameters including LVEF (AUC 0.79, 95% CI 0.67–0.91, and 0.81 [0.69–0.93]), left ventricular scar (0.87 [0.77–0.96] and 0.76 [0.63–0.89]), scar mass (0.84 [0.74–0.95] and 0.79 [0.67–0.91]), and microvascular obstruction (0.72 [0.56–0.87] and 0.71 [0.55–0.86]), respectively. Exploratory analyses linked only hsTnT and NT-proBNP to changes in CMR parameters.

Conclusions: Baseline hsTnT and NT-proBNP showed strong associations with 30-day CMR parameters after STEMI, whereas CCN1 and PCSK9 provided no discriminatory value in this intermediate post-infarction stage.

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1. Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity in adults worldwide [1,2]. Clinical presentations of acute coronary syndrome (ACS) vary with STEMI among the most urgent entities requiring timely coronary revascularization [3]. CMR enables comprehensive assessment of cardiac structure, function, and myocardial tissue injury after reperfused STEMI [4].

In the acute setting, novel circulating biomarkers may contribute to early risk stratification [3] and may predict CMR parameters and adverse clinical outcomes [5–8] potentially providing novel means for personalized treatment and risk assessment [9–11]. However, their ability to predict 30-day CMR derived infarct characteristics remains insufficiently characterized. CMR performed at 30 days may capture an intermediate phase between acute myocardial injury and the later chronic infarct state, thereby reflecting an intermediate post-infarction stage and potentially providing additional insight into the early trajectory of infarct healing and ventricular remodeling [4]. In this context, hsTnT and NT-proBNP represent established biomarkers of myocardial injury severity and cardiac stress after STEMI [3].

Cellular communication network factor 1 (formerly known as cysteine-rich angiogenic inducer 61) is a multifunctional matricellular protein involved in physiological and pathological processes, including tissue injury repair, angiogenesis, fibrosis, and atherosclerosis. CCN1 is responsive to multiple stimuli relevant to myocardial injury and repair, including hypoxia, mechanical stretch, inflammatory cytokines, and growth factors [12–14]. Increased cardiac CCN1 expression was found in patients with ischemic cardiomyopathy [15] and was shown to promote the transition of fibroblasts to a senescent phenotype, limiting cardiac fibrosis [16].

In an experimental myocardial infarction model CCN1-knockout mice showed diminished local alignment and heightened tortuosity of collagen fibers, reduced organizational coherency, packing and size of collagen fibrils impacting scar integrity [17].

Our group previously demonstrated that CCN1 serum levels correlate with final infarct size, even when classic cardiac biomarkers were still in their normal range, suggesting that CCN1 is an early biomarker of myocardial injury [18]. In patients with ACS, CCN1 was identified as a circulating biomarker predictive of recurrent myocardial infarction and mortality [8,19]. CCN1 levels measured at the onset of STEMI were significantly linked to infarct size and left ventricular end-diastolic volume (LVEDV) one year later, indicating that CCN1 may serve as an independent biomarker that adds prognostic value beyond conventional cardiac biomarkers [20]. However, the value of baseline CCN1 levels for predicting intermediate-term CMR-derived infarct characteristics after STEMI has not been established.

Proprotein convertase subtilisin/kexin 9 (PCSK9) is a key regulator of cholesterol metabolism, inducing lysosomal degradation of the LDL receptor in the liver [21]. The LDL receptor clears LDL cholesterol from circulation and antibody-based PCSK9 inhibition is successfully used to reduce cholesterol levels and to mitigate atherosclerotic cardiovascular disease [21]. Experimental data suggest that cardiomyocytes secrete PCSK9 during ischemic injury and that PCSK9 may contribute to infarct size development, cardiac dysfunction, and autophagy [22]. In STEMI patients, PCSK9 levels measured 48 h after infarction were significantly associated with intramyocardial hemorrhage, microvascular obstruction (MVO), infarct size, and adverse clinical outcomes [23].

Thus, hsTnT and NT-proBNP represent established biomarkers of myocardial injury and cardiac stress, whereas CCN1 and PCSK9 may reflect complementary biological pathways related to myocardial repair, scar formation, and microvascular injury. This study aimed to investigate the association of baseline serum levels of CCN1, NT-proBNP, hsTnT, and PCSK9 with CMR-derived infarct characteristics assessed 30 days after acute STEMI in the intermediate post-infarction stage.

2. Methods

2.1. Patients

This study included patients from the Controlled Level Everolimus in Acute Coronary Syndromes (CLEVER-ACS) randomized controlled trial, which comprised 150 patients presenting with acute STEMI between 2014 and 2021.

Routine blood samples were collected at all Swiss centers 12–24 h after coronary catheterization. The baseline CMR was performed 12 h – 5 days after primary PCI and the follow-up CMR 30 days after PCI. In the current pre-specified analysis the discriminatory performance of biomarkers at baseline for functional and structural parameters detected by CMR at 30 days was assessed [24].

2.2. Cardiac magnetic resonance

CMR was used to determine infarct characteristics at baseline (12 h to 5 days after PCI) and 30-day follow-up: Left ventricular ejection fraction (LVEF), scar mass, left ventricular scar (LV Scar), left ventricular end-systolic volume (LVESV), left ventricular end-systolic volume index (LVESVi), left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic diameter index (LVEDDi), LVEDV, left ventricular end-diastolic volume index (LVEDVi), left ventricular microvascular obstruction (LVMVO), microvascular obstruction (MVO), left ventricular end-systolic diameter (LVESD), left ventricular end-systolic diameter index (LVESDi), left ventricular stroke volume (LVSV), left ventricular stroke volume index (LVSVi), left ventricular mass (LVM), left ventricular mass index (LVMi) and scar slices [24].

Informed consent was obtained from all patients and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local ethics committees at all recruiting centers (University Hospital Bern, University Hospital Zurich, University Hospital Geneva and Cardiocentro Ticino in Lugano) [24].

2.3. Biomarkers

Blood samples were collected 12–24 h after PCI and immediately centrifuged, aliquoted, and stored at -80°C . Aliquots of EDTA plasma, heparinized plasma, and serum were prepared. High-sensitivity cardiac troponin T (hsTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured centrally at the Department of Clinical Chemistry, University Hospital Zurich, Zurich, Switzerland, using the cobas e801 system and immunoassays from Roche Diagnostics (Rotkreuz, Switzerland). CCN1 and PCSK9 concentrations were measured in duplicate in stored serum aliquots after thawing using ELISA-based immunoassays (Quantikine ELISA, R&D Systems, Minneapolis, MN, USA) [24].

2.4. Statistical analyses

Baseline characteristics of the study population are presented as medians with interquartile ranges for continuous variables due to the non-normal distribution of the data. Categorical variables are expressed as frequencies and percentages. Changes between baseline and follow-up were assessed using the Wilcoxon signed-rank test. Relative changes (delta values) between baseline (BL) and follow-up (FU) were calculated as $\Delta = (\text{FU} - \text{BL})/\text{BL} \times 100$. Associations between baseline biomarker concentrations and 30-day CMR parameters were assessed using Spearman correlation and summarized in a correlation matrix. Significant correlations were further examined using scatterplots with spline-based regression [25]. A p value of < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were calculated for significant biomarker-CMR associations to assess discriminatory performance.

In a separate exploratory approach, baseline biomarker concentrations were additionally correlated with relative changes in CMR parameters using a separate Spearman-based correlation matrix.

All statistical analyses were carried out using the statistical software R (v4.1.1, R Foundation for Statistical Computation, Vienna, Austria).

3. Results

3.1. Baseline characteristics

We identified 56 patients with available serum concentrations of all four biomarkers and complete baseline and 30-day follow-up CMR after STEMI. The study population had a median age of 59.9 (IQR 51.9–68.0) years and was predominantly male (89.3%). Patients had a median BMI of 26.2 (IQR 23.6–28.7) kg/m², 50.0% were active smokers, 48.2% had hypercholesterolemia, and 25.0% had pre-existing coronary artery disease. Further baseline characteristics are shown in [Table 1](#).

3.2. Associations between baseline biomarkers and CMR parameters

Baseline hsTnT and NT-proBNP showed significant and consistent associations with multiple 30-day CMR parameters after STEMI, including LVEF, scar mass, LV Scar, LVESV, MVO, and LVMVO. CCN1 was significantly associated with LVEF, whereas PCSK9 was not significantly associated with any CMR parameter. All significant correlations showed a consistent direction of effect.

NT-proBNP was significantly associated with LVEDDi, LVEDVi and LVESDi, but not with LVEDD, LVEDV, or LVESD. LVSV and LVSVi were associated only with NT-proBNP, whereas LVMi was only associated with hsTnT. Overall, the strongest correlation pattern was found for hsTnT, with $p < 0.001$ for LVEF, scar mass, LV Scar, LVESV, LVESVi,

Table 1
Baseline characteristics.

Patient Characteristics	Median or number of patients	IQR or percentage	Data availability
Median Age (years)	59.9	51.9 – 68.0	56/56
Median Creatinine (μmol/l)	82.0	72.0 – 92.0	53/56
Median BMI (kg/m ²)	26.2	23.6 – 28.7	56/56
Male Patients (n)	50	89.3%	56/56
Biomarker Concentrations			
hsTnT (pg/ml)	1410	144 – 2680	56/56
NT-proBNP (pg/ml)	910	109 – 1710	56/56
CCN1 (pg/ml)	128	107 – 149	56/56
PCSK9 (ng/ml)	304	245 – 363	56/56
Comorbidities			
Hypertension (n)	20	35.7%	56/56
Diabetes Mellitus (n)	4	7.14%	56/56
Cholesterolemia (n)	27	48.2%	56/56
Active Smoker (n)	28	50.0%	56/56
Ex-Smoker (n)	9	16.1%	56/56
Coronary artery disease (n)	14	25.0%	56/56
Medication			
Betablocker (n)	37	68.5%	54/56
ACE-Inhibitor (n)	38	70.4%	54/56
AT II Receptor Inhibitor (n)	6	11.1%	54/56
Statins (n)	45	83.3%	54/56
Diuretics (n)	13	24.1%	54/56
ASS (n)	51	94.4%	54/56
Clopidogrel (n)	6	11.1%	54/56
Prasugrel (n)	34	63.0%	54/56
Ticagrelor (n)	12	22.2%	54/56
Anticoagulation (n)	6	11.1%	54/56

[Table 1](#) shows the baseline characteristics, comorbidities and medication of the study population. Demographic and clinical variables are presented as medians with interquartile ranges (IQR) or counts (n) with corresponding percentage and data availability.

LVEDD, LVEDV, LVEDVi, LVESD and LVESDi. Further details of the correlation matrix with R-values are shown in [Fig. 1](#).

Scatterplots with spline-based regression supported the patterns previously identified using Spearman correlation. Exemplary scatterplots are provided in [Supplementary Fig. S1](#).

3.3. Exploratory associations with changes in CMR parameters from baseline to 30 days

Baseline hsTnT showed significant correlations with changes in LVEF, scar mass, LV Scar, LVEDDi, LVMVO, and MVO from baseline to 30 days. NT-proBNP showed a similar pattern but was not associated with changes in LV Scar. However, NT-proBNP was additionally associated with changes in LVEDD. In contrast, CCN1 and PCSK9 showed no significant correlations with any CMR parameter changes. Associations of hsTnT and NT-proBNP with changes in LVMVO from baseline to 30 days (hsTnT: Rsp = -0.35, $P < 0.01$; NT-proBNP: Rsp = -0.41, $P < 0.01$) were stronger than the corresponding associations with 30-day LVMVO values alone (hsTnT: Rsp = 0.29, $P < 0.05$; NT-proBNP: Rsp = 0.36, $P < 0.01$). Associations of hsTnT and NT-proBNP with changes in MVO from baseline to 30 days (hsTnT: Rsp = -0.39, $P < 0.01$; NT-proBNP: Rsp = -0.45, $P < 0.001$) were also stronger than the corresponding associations with 30-day MVO values alone (hsTnT: Rsp = 0.34, $P < 0.05$; NT-proBNP: Rsp = 0.34, $P < 0.01$). Correlation matrices of the delta changes model are displayed in [Supplementary Fig. S2](#).

3.4. Discrimination of CMR parameters at 30 days

In ROC analysis, baseline hsTnT showed the strongest discriminatory performance for CMR parameters at 30 days. hsTnT consistently achieved high AUC values, with peak values of 0.86, 95% CI:0.76 – 0.96 for LVESVi and 0.87, 95% CI:0.77 – 0.96 for LV Scar and AUC values of ≥ 0.8 also for scar mass, LVESV and LVEDVi. Similarly, NT-proBNP showed high AUC values, especially for LVEF (0.81, 95% CI:0.69 – 0.93), scar mass (0.79, 95% CI:0.67 – 0.91) and LVESVi (0.72, 95% CI:0.59 – 0.86).

Overall, AUC values were lower for CCN1 and PCSK9. CCN1 achieved its highest AUC value for LVEF with an AUC = 0.69, 95% CI:0.55 – 0.84. PCSK9 overall showed the lowest AUC values. AUC values are summarized in [Table 2](#). ROC analyses for LVEF, LV Scar, scar mass and MVO are shown in [Figs. 2a-d](#). ROC analyses for all other parameters are shown in [Supplementary Fig. S3](#).

4. Discussion

In this multi-biomarker study, baseline levels of hsTnT and NT-proBNP showed good discriminatory performance for clinically relevant CMR parameters at 30 days after STEMI.

In our previous 12-month follow-up study, different biomarkers including hsTnT, CCN1 and NT-proBNP were examined regarding their prognostic accuracy for changes in CMR parameters after STEMI [20]. In that long-term setting, baseline hsTnT emerged as the strongest predictor, while CCN1 showed prognostic value for structural, scar related and functional parameters.

The recommended timing for CMR endpoint assessment in post-infarction trials is 3–7 days after reperfusion, when key parameters such as late gadolinium enhancement and MVO are relatively stable [4]. In contrast, the present 30-day analysis reflects a biologically distinct phase of infarct healing, situated between acute myocardial injury and the later chronic infarct state, when scar maturation and ventricular remodeling are still evolving [26]. This intermediate time point may therefore complement, rather than replace, early and long-term follow-up by characterizing the evolving post-infarction tissue. At this intermediate time point, baseline hsTnT again demonstrated the strongest discriminatory performance.

The difference in timing may also explain why CCN1, which appears

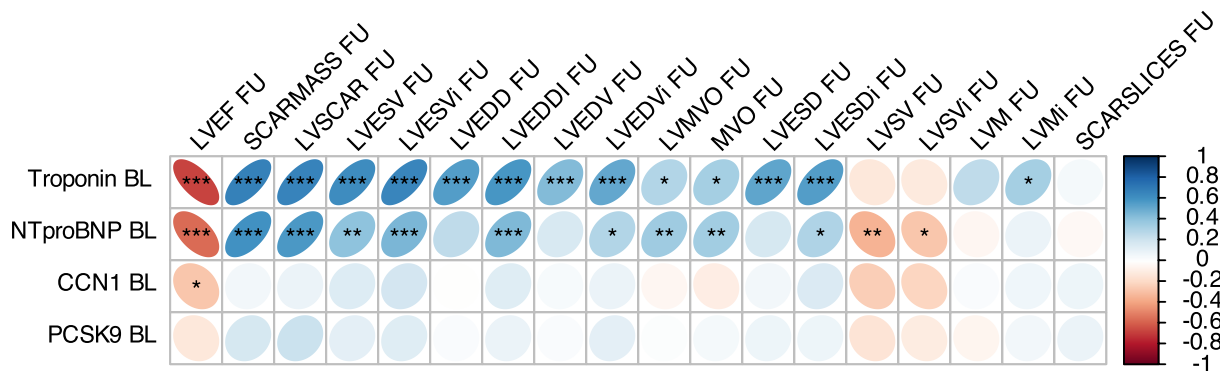


Fig. 1a. Correlation matrix showing relationship between baseline biomarker concentrations and follow-up parameters at 30-day follow-up after STEMI. Spearman correlation was used and statistical significance is indicated by asterisks: *p < 0.05, **p < 0.01, ***p < 0.001.

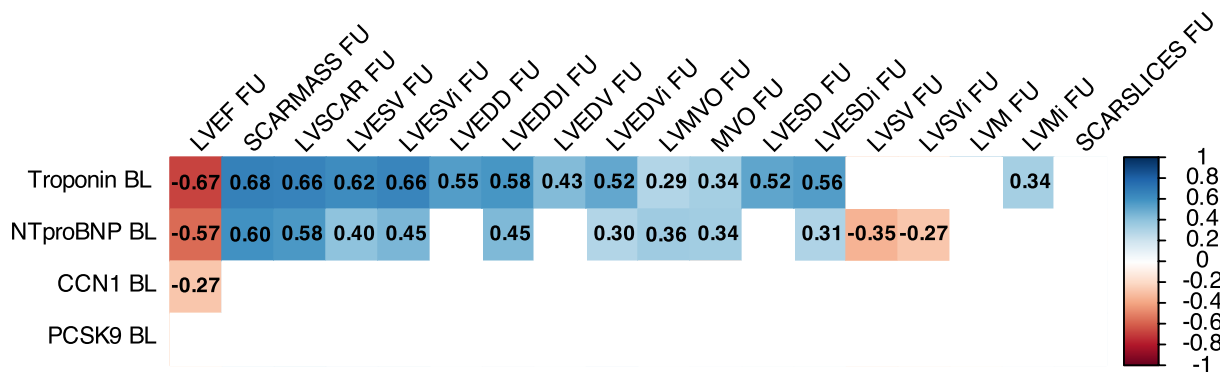


Fig. 1b. Correlation matrix showing relationship between baseline biomarker concentrations and follow-up parameters at 30-day follow-up after STEMI. Spearman correlation was used, with correlation coefficients (R values) displayed for each pairwise significant comparison. Key abbreviations: Troponin BL – High Sensitivity Troponin T Baseline; NT-proBNP BL – N-terminal Pro Brain Natriuretic Peptide Baseline; CCN1 BL – Cellular Communication Network Factor 1 Baseline; PCSK9 BL – Proprotein Convertase Subtilisin/Kexin Type 9 Baseline; LVEF – Left Ventricular Ejection Fraction; SCARMASS – Scar Mass; LV Scar – Left Ventricular Scar; LVESV – Left Ventricular End-Systolic Volume; LVESVi – Left Ventricular End-Systolic Volume Index; LVEDD – Left Ventricular End-Diastolic Diameter; LVEDDI – Left Ventricular End-Diastolic Diameter Index; LVEDV – Left Ventricular End-Diastolic Volume; LVEDVi – Left Ventricular End-Diastolic Volume Index; LVMVO – Left Ventricular Microvascular Obstruction; MVO – Microvascular Obstruction; LVESD – Left Ventricular End-Systolic Diameter; LVESDi – Left Ventricular End-Systolic Diameter Index; LVSV – Left Ventricular Stroke Volume; LVSVi – Left Ventricular Stroke Volume Index; LVM – Left Ventricular Mass; LVMi – Left Ventricular Mass Index; SCARSLICES – Scar Slices.

to be more closely linked to later phases of remodeling and collagen cross-linking, showed weaker associations in the present study compared to our previous long-term analysis [20].

Nguyen et al. examined the optimal timepoint for hsTnT measurements to predict infarct scar characteristics and LV function measured by CMR at a median of 4 days after STEMI [27]. They identified 48 to 72 h, corresponding to the plateau phase of hsTnT levels after STEMI, as the optimal timepoint [27]. Despite the differences in study design and timing, the findings on the predictive capability of hsTnT were consistent with ours. We also found hsTnT to be a strong predictor of infarct size, LVEF and MVO.

Mohammad et al. found peak hsTnT to predict long-term (1-year follow-up) LVEF [28]. Our data extend this finding with baseline hsTnT also predicting intermediate post-infarct LVEF (30-day follow-up).

In contrast, a large study from McLeod et al., including 3,698 patients, reported poor predictive value of hsTnT for excluding LV dysfunction, defined as an LVEF below 40%. They further noted that hsTnT levels overlapped across different degrees of myocardial dysfunction [29]. However, our analysis showed a strong correlation between hsTnT and LVEF. Overall, hsTnT emerged as the best-performing biomarker in our study, demonstrating significant associations and strong discriminatory performance with multiple parameters, including LVEF, scar mass, and MVO. Infarct size / late gadolinium enhancement is considered a primary CMR endpoint by expert panels, whereas LVEF and MVO are recommended as major secondary

endpoints and LV volumes may also serve as secondary outcome measures. Thus, our findings are not confined to scar-related measures, but extend to clinically relevant and pathophysiologically functional, volumetric, and microvascular parameters [4].

These findings support hsTnT as a clinically relevant marker in STEMI patients [5–8], with potential value for early risk stratification [9–11], as it reflects CMR-based changes and may provide insight into the early trajectory of infarct healing.

NT-proBNP was recently found to be associated with 3-year rates of major adverse cardiovascular events in NSTEMI patients [30], supporting its role in ACS patients. Steen et al. measured NT-proBNP and cardiac troponin T 96 h after acute myocardial infarction and found significant correlations with CMR-derived infarct size and LVEF. NT-proBNP correlated more closely with LVEF than troponin T, whereas troponin T correlated more closely with infarct size than NT-proBNP. In our study of STEMI patients, NT-proBNP was significantly associated with a wide range of clinically relevant CMR parameters. For LVEF and LVMVO, NT-proBNP yielded the highest AUC values among the investigated biomarkers. Consistent with Steen et al [31], NT-proBNP showed higher AUC values for LVEF than hsTnT in the present study. Conversely, hsTnT showed higher AUC values for LV Scar than NT-proBNP. Taken together, these findings suggest that NT-proBNP and hsTnT reflect overlapping but not identical aspects of the 30-day post-infarction CMR parameters, with NT-proBNP showing closer associations with functional parameters and hsTnT with scar-related injury

Table 2
Results of receiver operating characteristics and Area under the curve values.

	hsTnT AUC (95%CI)	NT-proBNP AUC (95% CI)	CCN1 AUC (95% CI)	PCSK9 AUC (95% CI)
LVEF	AUC = 0.79 (0.67 – 0.91)	AUC = 0.81 (0.69 – 0.93)	AUC = 0.69 (0.55 – 0.84)	AUC = 0.55 (0.39 – 0.70)
Scar mass	AUC = 0.84 (0.74 – 0.95)	AUC = 0.79 (0.67 – 0.91)	AUC = 0.5 (0.34 – 0.66)	AUC = 0.59 (0.43 – 0.74)
LV Scar	AUC = 0.87 (0.77 – 0.96)	AUC = 0.76 (0.63 – 0.89)	AUC = 0.50 (0.35 – 0.66)	AUC = 0.59 (0.44 – 0.74)
LVESV	AUC = 0.84 (0.73 – 0.94)	AUC = 0.69 (0.54 – 0.83)	AUC = 0.60 (0.45 – 0.75)	AUC = 0.58 (0.43 – 0.73)
LVESVi	AUC = 0.86 (0.76 – 0.96)	AUC = 0.72 (0.59 – 0.86)	AUC = 0.59 (0.44 – 0.75)	AUC = 0.58 (0.43 – 0.73)
LVEDD	AUC = 0.71 (0.57 – 0.85)	AUC = 0.58 (0.43 – 0.74)	AUC = 0.50 (0.34 – 0.65)	AUC = 0.52 (0.36 – 0.67)
LVEDDi	AUC = 0.79 (0.66 – 0.91)	AUC = 0.71 (0.57 – 0.85)	AUC = 0.51 (0.35 – 0.66)	AUC = 0.51 (0.36 – 0.67)
LVEDV	AUC = 0.69 (0.55 – 0.84)	AUC = 0.55 (0.40 – 0.70)	AUC = 0.52 (0.37 – 0.67)	AUC = 0.51 (0.35 – 0.66)
LVEDVi	AUC = 0.83 (0.72 – 0.94)	AUC = 0.70 (0.56 – 0.84)	AUC = 0.58 (0.43 – 0.73)	AUC = 0.55 (0.39 – 0.71)
LVMVO	AUC = 0.69 (0.53 – 0.85)	AUC = 0.73 (0.57 – 0.88)	AUC = 0.54 (0.37 – 0.72)	AUC = 0.53 (0.35 – 0.71)
MVO	AUC = 0.72 (0.56 – 0.87)	AUC = 0.71 (0.55 – 0.86)	AUC = 0.59 (0.41 – 0.76)	AUC = 0.51 (0.34 – 0.69)
LVESD	AUC = 0.70 (0.56 – 0.84)	AUC = 0.55 (0.39 – 0.71)	AUC = 0.53 (0.37 – 0.68)	AUC = 0.51 (0.35 – 0.67)
LVESDi	AUC = 0.76 (0.63 – 0.88)	AUC = 0.58 (0.43 – 0.74)	AUC = 0.60 (0.45 – 0.75)	AUC = 0.52 (0.37 – 0.68)
LVSV	AUC = 0.59 (0.44 – 0.74)	AUC = 0.66 (0.51 – 0.8)	AUC = 0.59 (0.43 – 0.74)	AUC = 0.59 (0.44 – 0.75)
LVSVi	AUC = 0.52 (0.36 – 0.67)	AUC = 0.57 (0.42 – 0.73)	AUC = 0.68 (0.53 – 0.82)	AUC = 0.60 (0.44 – 0.76)
LVM	AUC = 0.68 (0.53 – 0.82)	AUC = 0.57 (0.41 – 0.72)	AUC = 0.51 (0.35 – 0.66)	AUC = 0.55 (0.39 – 0.7)
LVMi	AUC = 0.67 (0.52 – 0.81)	AUC = 0.60 (0.45 – 0.76)	AUC = 0.53 (0.37 – 0.69)	AUC = 0.52 (0.37 – 0.68)
Scar slices	AUC = 0.51 (0.34 – 0.67)	AUC = 0.52 (0.36 – 0.68)	AUC = 0.53 (0.37 – 0.68)	AUC = 0.54 (0.39 – 0.70)

Table 2 providing Area Under the Curve (AUC) values with 95% confidence intervals (CIs) from receiver operating characteristic (ROC) analyses for various CMR parameters in relation to CCN1, PCSK9, hsTnT, and NT-proBNP. The parameters assessed include LVEF- Left Ventricular Ejection Fraction; SCARMASS – Scar Mass; LV SCAR – Left Ventricular Scar; LVESV- Left Ventricular End-Systolic Volume; LVESVi – Left Ventricular End-Systolic Volume Index; LVEDD – Left Ventricular End-Diastolic Diameter; LVEDDi – Left Ventricular End-Diastolic Diameter Index; LVEDV – Left Ventricular End-Diastolic Volume; LVEDVi – Left Ventricular End-Diastolic Volume Index; LVMVO – Left Ventricular Microvascular Obstruction; MVO – Microvascular Obstruction; LVESD – Left Ventricular End-Systolic Diameter; LVESDi – Left Ventricular End-Systolic Diameter Index; LVSV – Left Ventricular Stroke Volume; LVSVi – Left Ventricular Stroke Volume Index; LVM – Left Ventricular Mass; LVMi – Left Ventricular Mass Index; SCARSLICES – Scar Slices. AUC values indicate the diagnostic performance of each parameter for distinguishing relevant biomarker levels, with higher values reflecting better discriminative ability.

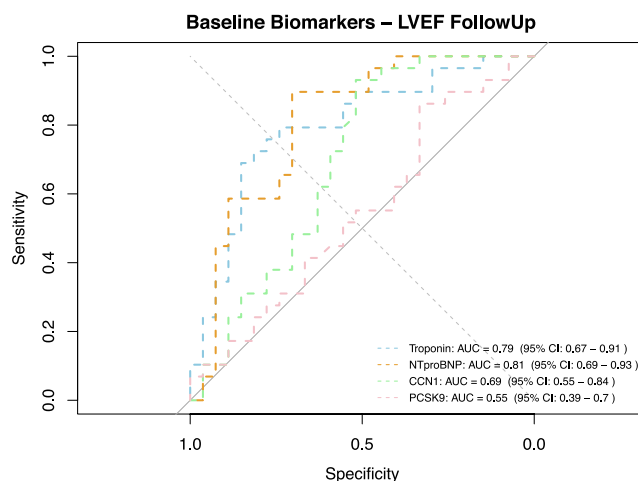


Fig. 2a. Receiver operating characteristic (ROC) curve for baseline high sensitivity troponin T, N-terminal Pro Brain Natriuretic Peptide, Cellular Communication Network Factor 1 and Proprotein Convertase Subtilisin/Kexin Type 9 predicting dichotomized left ventricular ejection fraction (LVEF), 30-days after STEMI. The plot displays the sensitivity and specificity of the baseline biomarker concentrations in predicting dichotomized LVEF, with the area under the curve (AUC) indicating the prognostic value.

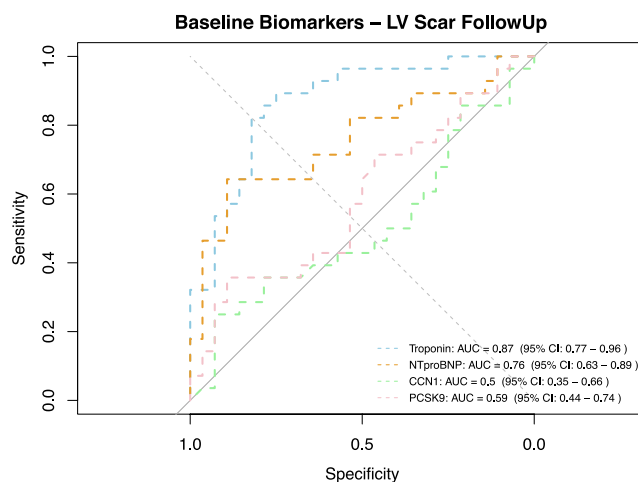


Fig. 2b. Receiver operating characteristic (ROC) curve for baseline high sensitivity troponin T, N-terminal Pro Brain Natriuretic Peptide, Cellular Communication Network Factor 1 and Proprotein Convertase Subtilisin/Kexin Type 9 predicting dichotomized left ventricular scar (LV Scar), 30-days after STEMI. The plot displays the sensitivity and specificity of the baseline biomarker concentrations in predicting dichotomized LV Scar, with the area under the curve (AUC) indicating the prognostic value.

characteristics.

In our previous study, baseline CCN1 levels in STEMI patients were significantly associated with LVEDV and infarct size at 12 months measured by CMR [20], supporting its potential as a long-term ventricular remodeling biomarker. Our group also found CCN1 to be an early marker of myocardial injury, correlating with peak CK-MB, as a surrogate for infarct size, even when hsTnT was not elevated yet [18]. CCN1 was also significantly associated with short-term post-infarction LVEF measured by TTE at a median of 3 days after PCI [18].

In contrast, our present 30-day analysis reflects an intermediate phase of infarct healing, when early fibrotic replacement has largely occurred, and scar maturation and collagen cross-linking are ongoing [26]. At this time point, associations with LVEDV and infarct size could not be observed. However, the significant association with short-term

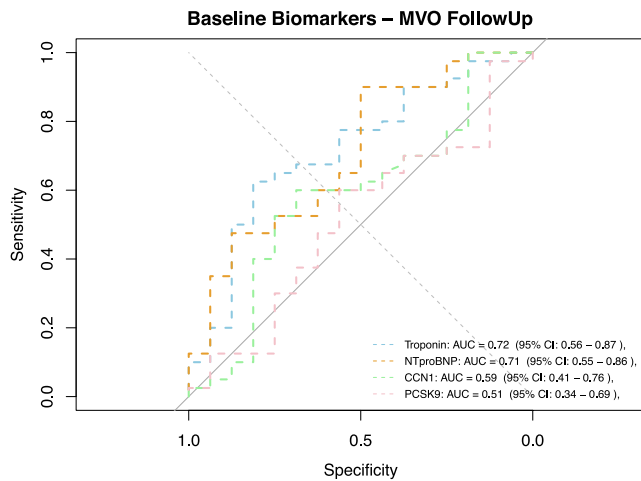


Fig. 2c. Receiver operating characteristic (ROC) curve for baseline high sensitivity troponin T, N-terminal Pro Brain Natriuretic Peptide, Cellular Communication Network Factor 1 and Proprotein Convertase Subtilisin/Kexin Type 9 predicting dichotomized microvascular obstruction (MVO), 30-days after STEMI. The plot displays the sensitivity and specificity of the baseline biomarker concentrations in predicting dichotomized MVO, with the area under the curve (AUC) indicating the prognostic value.

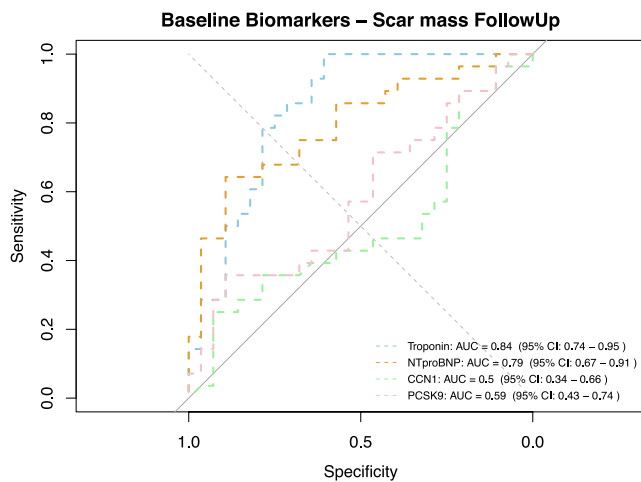


Fig. 2d. Receiver operating characteristic (ROC) curve for baseline high sensitivity troponin T, N-terminal Pro Brain Natriuretic Peptide, Cellular Communication Network Factor 1 and Proprotein Convertase Subtilisin/Kexin Type 9 predicting dichotomized Scar mass, 30-days after STEMI. The plot displays the sensitivity and specificity of the baseline biomarker concentrations in predicting dichotomized Scar mass, with the area under the curve (AUC) indicating the prognostic value.

post-infarction LVEF persisted at 30 days. These findings suggest that CCN1 is not a suitable biomarker for intermediate-term assessment of scar-related structural changes at 30 days but could become relevant for later remodeling stages and final infarct size.

This interpretation is supported by experimental evidence from fibroblast-specific CCN1 knockout mice, in which loss of CCN1 did not alter overall collagen content or ventricular performance, but resulted in disorganized collagen fibril architecture, increased matrix compliance, and higher rates of cardiac rupture after infarction [17]. These findings support that CCN1 is important for coordinated collagen alignment and structural stability of the developing scar, suggesting a potential mechanistic link to extracellular matrix organization during infarct maturation [17].

Overall, these findings suggest that CCN1 may reflect dynamic

aspects of later remodeling rather than intermediate-term infarct repair.

For PCSK9, we did not observe meaningful discriminatory performance for CMR parameters at 30 days, which aligns with previous findings by Tiller et al [23], who reported that PCSK9 measurements within the first 24 h were not significantly associated with myocardial or microvascular injury. In serial measurements, Tiller et al. observed an increase in PCSK9 levels between 24 and 48 h after STEMI and PCSK9 levels after 48 h were significantly associated with intramyocardial hemorrhage, MVO, infarct size and worse clinical outcomes. Thus, our negative findings for baseline PCSK9 do not exclude a role of PCSK9 in post-infarction tissue injury, but rather suggest that its association with myocardial and microvascular damage may depend on later measurement time points.

4.1. Limitations

The number of patients in our multi-center study was limited to 56 patients. The present analysis constitutes a pre-specified substudy of the randomized controlled CLEVER-ACS trial, which is one of the largest studies in the field. This substudy included patients who were well characterized by baseline and 30-day follow-up CMR, including MVO and LVMVO using a core lab. Furthermore, all biomarkers were centrally analyzed. Treatment allocation occurred in a double-blind manner as part of the randomized controlled trial design of CLEVER-ACS. However, some degree of selection bias cannot be fully excluded because participation in the substudy was restricted to Swiss patients with complete biomarker and CMR follow-up data. The marked male predominance limits generalizability, particularly with regard to female STEMI patients, although this imbalance reflects the underlying CLEVER-ACS population.

5. Conclusion

Baseline levels of hsTnT and NT-proBNP are strong predictors of functional and dimensional CMR parameters of the left ventricle including clinically relevant imaging surrogates of myocardial injury 30 days after STEMI. CCN1 and PCSK9 showed no associations in this intermediate phase of infarct healing.

6. Note

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

CRediT authorship contribution statement

Tim Horbach: Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Florian A. Wenzl:** Writing – review & editing, Visualization, Investigation, Formal analysis, Data curation. **Robert Manka:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Lorenz Rüber:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization. **David Carballo:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis. **Till Keller:** Writing – review & editing, Supervision, Project administration, Methodology. **Samuel Sossalla:** Writing – review & editing, Supervision, Resources. **Frank Ruschitzka:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Arnold von Eckardstein:** Writing – review & editing, Supervision, Resources, Project administration, Methodology. **Barbara E. Stähli:** Writing – review & editing, Supervision, Project administration, Investigation. **Thomas F. Lüscher:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Roland Klingenberg:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration,

Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2026.101918>.

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