

ORIGINAL RESEARCH



Importance of myocardial ischemia detected with protocol-based measurements of high-sensitivity troponin, ECG and echocardiography in critically ill patients without acute coronary syndrome—a prospective study

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Abstract

Elevated cardiac troponin is detected in the majority of critically ill patients. This study aimed to evaluate the prognostic value of protocol-guided detection of myocardial ischemia (MI) (serial 12-lead electrocardiograms (ECG), high-sensitivity troponin T (hsTnT) measurements, and echocardiography) and compare it with a retrospective cohort with only clinically driven detection of MI. In a prospective observational study, 95 patients hospitalized ≥ 48 hours for reasons other than acute coronary syndrome in medical or surgical intensive-care unit (ICU) were enrolled. A protocol-based approach, with regular 12-lead ECG recordings, hsTnT measurements and admission echocardiography was conducted. All events possibly indicating MI were documented, and ECG, hsTnT, echocardiography were repeated. The protocol-based approach was compared to a retrospective group with only clinically driven detection of MI. In the prospective group, 95.8% of patients had at least one elevated hsTnT value. A hsTnT >70 ng/L was associated with the use of inotropes (OR 3.35 (95% CI: 1.184, 9.472), $p = 0.022$), left ventricular ejection fraction $<30\%$ (OR 9.65 (95% CI: 1.172, 76.620), $p = 0.035$), regional wall motion abnormalities (OR 3.87 (95% CI: 1.032, 14.533), $p = 0.045$), ICU mortality (OR 8.38 (95% CI: 1.004, 69.924), $p = 0.0495$), hospital mortality (OR 3.05 (95% CI: 1.133, 8.230), $p = 0.027$) and 1-year mortality (OR: 5.43 (95% CI: 2.1099, 13.971), $p = 0.005$). The incidence of MI was higher in the prospective, as compared to the retrospective group (22.1% vs 5.3%; $p = 0.001$). MI, compared to the high “hsTnT positive only” group, predicted hospital mortality (OR 3.33 (95% CI: 1.190, 9.329), $p = 0.02$) and 1-year mortality (OR 4.66 (95% CI: 1.647, 13.222), $p = 0.0037$). A protocol-based compared to a clinically driven approach for the detection of MI reveals more patients with MI. The majority of critically ill patients have elevated hsTnT levels. Detected MI additionally stratifies patients with elevated hsTnT to higher hospital and 1-year mortality.

Keywords

Critically ill; Troponin; Outcome; Mortality; ECG; Echocardiography

1. Introduction

Cardiac troponins (cTn) are regulatory proteins and part of the cardiomyocyte contractile apparatus. They are expressed almost exclusively in the heart and have been established as the preferred biomarker in diagnosing myocardial ischemia (MI) and injury as they have high myocardial tissue specificity and clinical sensitivity [1, 2]. Detection of reversible increase of cardiac biomarkers (preferably cTn) together with clinical signs of ischemia is the cornerstone of diagnosing myocardial infarction. cTn elevation without clinical signs of ischemia is

myocardial injury, which could be acute or chronic [1, 2].

Critically ill patients are at higher risk for MI due to their older age, underlying coronary artery disease, and other comorbidities. The heart is affected by intrinsic and extrinsic sympathetic stimulation, various other toxic mediators and stressors – anaemia, tachycardia, hypotension. MI in the critically ill may not always be apparent, and establishing a diagnosis is challenging [3]. Patient communication is limited and ischemic symptoms are often absent. ECG changes may not be detected or are non-specific, and elevated cTn levels, although common, are difficult to interpret in the context of

critical illness and other comorbidities [3–6]. Echocardiography and coronary angiography are not routinely performed in all patients with suspected MI. There are currently no diagnostic criteria or treatment strategies for detecting MI in the critically ill. New laboratory methods to detect low levels of cTn, i.e., high sensitivity troponin T (hsTnT) assays, are available. Their value in critically ill patients exhibiting no acute coronary syndrome is still not firmly defined.

The aim of our study was to evaluate a protocol-guided approach to detect MI in the critically ill (serial ECGs, hsTnT measurements, and echocardiography) in comparison to a retrospective cohort with only clinically driven detection of MI.

2. Methods

2.1 Setting

A prospective observational study was conducted in medical and surgical intensive care units (ICUs) in General and Teaching Hospital Celje, Slovenia during a 6-month period (from June to December 2017). Both units are level 3, adult 11 bed ICUs, covered 24/7 by intensive care specialists.

2.2 Patients

Critically ill adults hospitalized in the ICU for more than 48 hours, who gave, or whose family gave informed consent, were enrolled. Only patients who required life support for organ failure, monitoring and treatment (i.e., mechanical ventilation, renal replacement therapy, invasive hemodynamic monitoring [7]) were enrolled. Patients with a primary diagnosis of myocardial infarction (ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI)), patients younger than 18 years, pregnant women, patients admitted to the ICU for postoperative monitoring after major surgeries without complications, and patients admitted for elective pacemaker/defibrillator implantation were not included. Patients transferred from other hospitals were also not included.

2.3 Patient data

Basic demographic data were collected at admission. Known cardiovascular risk factors (ischaemic heart disease, hypertension, diabetes, vascular disease), chronic illnesses (atrial fibrillation, heart failure, chronic obstructive pulmonary disease (COPD), chronic renal disease), APACHE II score and admission diagnosis were recorded. We also recorded the use of vasopressors (noradrenaline, dopamine, vasopressin), inotropes (dobutamine, levosimendan) and mechanical ventilation during the ICU stay.

2.4 Protocol for detecting myocardial ischemia

Patients underwent a protocol-based prospective screening for the occurrence of MI. At admission, transthoracic echocardiography and standard 12-lead ECG were recorded and hsTnT was measured. During ICU stay, hsTnT measurement and 12-lead ECG were performed twice daily for the first week and then weekly until ICU discharge or death. All events (termed

“acute events”) possibly indicating the presence of MI were documented, and at that time, ECG, hsTnT and echocardiogram were repeated. Such events were: hypotension, new-onset arrhythmia (including cardio-pulmonary resuscitation (CPR)), increased need for vasopressors or inotropes, pulmonary oedema and chest pain. All study data were available to the ICU team to enable further diagnostic and therapeutic interventions.

2.5 Echocardiography

The transthoracic echocardiographic exam (Philips Sparq ultrasound, Philips, NL) was performed by the intensive care specialist. Left ventricular ejection fraction (LVEF), regional wall motion abnormalities (RWMA) and major valvular abnormalities were recorded. LVEF was classified as abnormal (<54%) and severely abnormal (<30%) [8].

2.6 High-sensitivity troponin T measurement

hsTnT levels were measured by high-sensitivity troponin T assay - Roche electro-chemiluminescent sandwich assay - Elecsys troponin T STAT (Roche Diagnostics, Switzerland). The cobas e 411 analyser (Roche Diagnostics, Switzerland) was used. The measuring range of the assay is 3–10,000 ng/L. The limit of blank is 3 ng/L, the limit of detection 5 ng/L, limit of quantification 13 ng/L. The upper reference limit (99th percentile) is 14 ng/L (95% CI: 12.7–24.9 ng/L). All laboratory analyses were performed in the department of laboratory diagnostics in General and Teaching Hospital Celje.

2.7 Diagnosing myocardial injury

hsTnT was considered as elevated if >14 ng/L. Serial 12-lead ECGs were interpreted by the researcher and the intensive care specialists. The diagnosis of MI was made according to the Third Universal Definition of myocardial infarction (Joint ESC/ACCF/AHA/WHF Task Force) - the presence of elevated levels hsTnT >14 ng/L and contemporary ECG changes, chest pain or new RWMA on transthoracic echocardiography. This definition was current at the time of the study [2]. Accordingly, patients were classified into groups: (1) patients with MI, (2) patients with elevated hsTnT levels only and (3) patients with no hsTnT elevation.

Regarding the maximal hsTnT level detected during hospitalization, patients were also classified into groups (1) hsTnT max >14 ng/L, (2) hsTnT max >52 ng/L, (3) hsTnT max >70 ng/L – the cut off values were made according to the prevailing NSTEMI guidelines for using hsTnT [9, 10].

2.8 Retrospective cohort

The prospective group was compared to the retrospective group, hospitalized at both ICUs in the 6-month period in the year 2016, where only clinical-driven diagnostic procedures were used to diagnose MI. We examined the patient charts, hsTnT levels determined on admission and during ICU stay, ECG recordings and echocardiograms performed. In charts, we searched for possible acute events and examined whether there were any further diagnostic measures made.

2.9 Primary outcome

Patients were followed up to one year after ICU admission. The primary outcomes were mortality at ICU discharge, at hospital discharge and one-year mortality. In the prospective group, the relationship between detected MI or elevated hsTnT with primary outcomes was explored.

2.10 Secondary outcome

Secondary outcomes were an exploration of the relationship between detected MI or elevated hsTnT with a need of an inotrope, LVEF <30% and RWMA.

2.11 Sample size estimation

A sample size of 80 patients (40 in each group) was determined for (type I error (α) 0.05 and power, type II error (β) 0.20) for detecting 1-year mortality difference. Mortality of 60% in the high hsTnT group compared to 30% in the low hsTnT/control group was assumed. MedCalc ver. 12.5 (MedCalc Software Ltd, Ostend, Belgium) was used for sample size estimation.

2.12 Statistical analysis

Data were summarized as mean (\pm standard deviation), or median (range), as expressed through minimum and maximum values, for metric variables, or absolute and relative frequencies for categorical variables. Tests for normal distributions did not reject the null hypothesis that the majority of variables were normally distributed. The student's *t*-test was used for metric variables and Chi-Square for categorical data. Correlation between variables was explored by using Pearson correlation. A receiver operating characteristic (ROC) curve analysis was used for testing the predictive ability of maximal hsTnT for ICU mortality. Odds ratios for MI and hsTnT >70 ng/L for predicting inotrope use, LVEF <30%, RWMA and mortality were calculated. The analyses were performed using SPSS v.25.0 software package (SPSS Inc., Chicago, IL, USA) and MedCalc ver. 12.5 (MedCalc Software Ltd, Ostend, Belgium). A *p*-value < 0.05 was considered to define statistical significance.

3. Results

3.1 Patient population

Over a six-month period, 95 patients who met the study inclusion criteria were identified, approached, and afterwards included. Over the same period in the previous year (2016), we found 94 patients for retrospective analysis. The comparison between groups is presented in Table 1.

In the prospective group, there were 46 medical and 49 surgical patients. The most prevalent admission diagnosis was septic shock (45.3%) while 11.6% of patients were admitted due to acute heart failure or cardiogenic shock. Other diagnoses included trauma, haemorrhagic shock, neurologic disability (head trauma, intracerebral haemorrhage) and acute respiratory failure (Table 2). In the retrospective group, there were 46 medical and 48 surgical patients. The most prevalent diagnosis in the retrospective group was septic shock (48.9%).

3.2 Comparing prospective and retrospective cohorts

A significantly higher number of patients with MI were diagnosed in the prospective group compared to the retrospective group (22.1% vs 5.3%; *p* = 0.001).

Due to the protocol, all patients in the prospective group had admission hsTnT levels measured, whereas, in the retrospective group, 12 patients who did not have any hsTnT levels were measured during their ICU stay (*p* = 0.006).

There were 24 acute events in the prospective group and 21 in the retrospective group. ECG, hsTnT levels and echocardiogram were repeated at all acute events in the prospective cohort, whereas in the retrospective group ECG was recorded at 4 events (*p* = 0.008), and both hsTnT and echocardiogram were repeated at 2 events (*p* = 0.001). ICU mortality was lower in the prospective group. There was no difference in in-hospital mortality between cohorts (Table 1).

4. Prospective group analysis

4.1 Baseline characteristics

There was no significant difference in APACHE II score between patients with MI and patients with only elevated hsTnT. Patients with hsTnT levels higher than thresholds of 52 ng/L and 70 ng/L had higher APACHE II scores than other patients (Table 2).

Patients with MI were older and had more comorbidities. Hypertension, heart failure, chronic kidney disease, vascular disease and diabetes were more common in these patients (Table 2). Previously diagnosed ischemic heart disease was not more common in patients whom we diagnosed with MI.

4.2 Troponin levels and myocardial ischemia

In the prospective group, 91 (95.8%) patients had at least one elevated hsTnT level and 21 (23.1%) of these patients met the diagnostic criteria of MI. Seventy patients (76.9% of patients with elevated hsTnT) had elevated hsTnT levels without other signs of MI. There were only 4 patients with hsTnT in the normal range.

All patients with MI had at least one hsTnT level higher than 70 ng/L. Moreover, they all had a maximal hsTnT level above 100 ng/L. Patients with MI had significantly higher maximal hsTnT level than those with elevated troponin levels only (1101.1 ± 1203.2 ng/L vs 184.1 ± 409.8 ng/L, *p* = 0.002), but at admission, the difference was not significant (344.4 ± 595.3 ng/L vs 75.00 ± 126.5 ng/L).

Nineteen of 21 (90.4%) patients with MI had ST depression, one had an intermittent right bundle branch block and high clinical suspicion for ischemia. He experienced cardiac arrest with successful CPR (P asystole, intermittent new right bundle branch block (RBBB)), and required a temporary and afterwards a permanent pacemaker. Only one patient experienced chest pain.

4.3 Echocardiographic abnormalities

Patients with MI had lower LVEF than patients with elevated hsTnT only ($45.9 \pm 15.3\%$ vs $56.9 \pm 13.4\%$; *p* = 0.002). A

TABLE 1. Prospective and retrospective group comparison.

	Prospective group	Retrospective group	<i>p</i> value
Age, mean (SD)	70.6 (11.6)	71.7 (13.7)	0.484
Female, (%)	32.6%	42.6%	0.159
APACHE II, mean (SD)	18.8 (7.9)	19.9 (7.2)	0.484
Detected MI, N (%)	21 (22.1%)	5 (5.3%)	0.001
ICU mortality, N (%)	9 (9.5%)	25 (26.6%)	0.002
Hospital mortality, N (%)	25 (26.3%)	35 (37.2%)	0.107

APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; SD, standard deviation; MI, myocardial ischemia; N, number.

weak inverse correlation between hsTnT and LVEF was found (Pearson correlation coefficient -0.303 , $p = 0.003$). LVEF $<30\%$ and RWMA were associated with high hsTnT levels and MI (Tables 3 and 4).

4.4 Primary outcomes

Patients with MI had higher in-hospital and one-year mortality (Table 4). There was no difference in ICU mortality between patients with MI and with elevated hsTnT only. Hospital mortality and one-year mortality were higher in patients with hsTnT levels above 52 ng/L. Maximal hsTnT levels, but not admission levels, were associated with ICU mortality (ROC curve: AUC 0.803; $p = 0.003$; sensitivity: 77.8%; specificity: 75.6%, cut off TnT value: 157.50 ng/L) (Fig. 1). Odds ratios of hsTnT >52 ng/L, hsTnT >70 ng/L and MI to predict outcome are presented in Table 5.

4.5 Treatment

Only 11 patients (52.4%) with MI were treated with standard anti-ischemic or antiplatelet drugs. Two patients underwent coronary angiography; in the first patient, NSTEMI was diagnosed with significant one vessel coronary disease treated with stent implantation, and in the second patient, there was no obstructive coronary disease. We did not find any difference in the use of vasopressors and mechanical ventilation between patients with MI and other patients. Odds ratio for use of inotrope in patients with hsTnT >70 ng/L was 3.348 (95% CI: 1.184–9.472, $p = 0.02$) (Table 5).

5. Discussion

Our study confirmed that elevated hsTnT levels are a very common finding in the critically ill. Maximal hsTnT levels during ICU stay can predict ICU, in-hospital and even one-year mortality. Elevated hsTnT levels in critically ill patients can predict the use of inotropes, echocardiographic abnormalities such as lower LVEF and RWMA. Standard diagnostic procedures and laboratory findings are not very effective in diagnosing MI in the critically ill, as we confirmed with our protocol-driven approach. Detected MI additionally stratifies patients with elevated hsTnT to higher hospital and one-year mortality.

In our study, all patients had detectable hsTnT levels during their ICU stay, and $>95\%$ of them had at least one elevated hsTnT level. To our knowledge, this is the highest reported percentage of patients with elevated cTn levels in the ICU – reflecting a new era of highly sensitive troponin assays [11, 12]. Almost a quarter of patients with elevated hsTnT levels also had other signs of MI (chest pain, ECG abnormalities). All patients with MI had hsTnT levels higher than 100 ng/L.

Diagnosing MI and interpreting elevated cTn levels in critically ill patients is challenging for various reasons, and applying the recent definition of myocardial infarction has its limitations [1, 2]. Communication with critically ill patients is hampered and ischemic chest pain is often masked by analgesic and sedative drugs [4, 6, 11]. Some MI-associated signs, such as hypotension, arrhythmia or pulmonary oedema, are non-specific and could be related to other diseases, such as sepsis or respiratory failure. Continuous ECG monitoring is not as sensitive as frequent 12-lead ECG recordings [13]. Moreover, ECG changes are frequently difficult to interpret, particularly in patients with a bundle branch block, electrostimulation or electrolyte disturbances [1]. The reliability of interpretation depends not only on the physician's knowledge and experience but also on the clinical information provided [14]. Our study confirmed that the most common ECG change suggesting MI in critically ill patients is ST depression [15, 16].

The rates of elevated cTn observed in previous studies were influenced by different study protocols and troponin assays used. In a meta-analysis of 20 studies, Lim *et al.* [17] found elevated cTn levels in 43% of 3278 patients. Ostermann *et al.*, [4] using a protocol-based approach with hsTnT, found that 84% of 144 patients had at least one elevated troponin level and 41% met the criteria for MI. Study results were blinded to ICU staff and only 20% of definite MIs were recognised by the clinical team. In a similar study, although with a third-generation Tn assay, Lim *et al.* [6] found that MI was present in 35.9% of 103 patients, 14.6% had elevated cTn levels only, and 49.5% had no cTn elevation.

Our results confirm that elevated hsTnT and MI are associated with higher in-hospital and even 1-year mortality. The relationship between cTn and mortality is not new [4, 5, 18], although, prior results are not all in agreement. Myocardial injury and MI have been associated with ICU and perioperative mortality [19] regardless of the aetiology of cTn release.

TABLE 2. Baseline prospective group characteristics.

Total (N = 95)	Myocardial ischemia (N = 21)	Elevated TnT only (N = 70)	hsTnT > 52 ng/L (N = 60)	hsTnT ≤52 ng/L (N = 35)	hsTnT >70 ng/L (N = 50)	HsTnT ≤70 ng/L (N = 45)	Statistics (p value)	
BASELINE CHARACTERISTICS								
Age, mean (SD)	70.5 (11.6)	75.4 (6.5)	69.9 (11.7)	74.1 (8.6)	65.7(13.2)	74.1 (8.6)	66.4 (13.1)	MI vs elevated hsTnT only: 0.007 hsTnT >52 ng/L vs others: 0.001 hsTnT >70 ng/L vs others: 0.001
APACHE II score, mean (SD)	18.8 (7.9)	20.1 (7.9)	18.6 (8.1)	21.1 (8.1)	15.2 (6.0)	21.1 (8.1)	16.3 (7.0)	MI vs elevated hsTnT only: 0.407 hsTnT >52 ng/L vs others: 0.001 hsTnT >70 ng/L vs others: 0.002
Female, N (%)	31 (32.6%)	8 (38.1%)	20 (28.6%)	8 (36.0%)	13 (37.1%)	18 (36.0%)	13 (28.9%)	MI vs elevated hsTnT only: 0.407
ADMISSION DIAGNOSIS								
Septic shock	43 (45.3%)	8 (38.1%)	35 (50.0%)	18 (30.0%)	/	10 (40.0%)	/	/
Cardiogenic shock	11 (11.6%)	4 (19.0%)	7 (10.0%)	26 (43.0%)		7 (14.0%)		
Other	41(43.2%)	9 (42.9%)	28 (40.0%)	9 (15.0%)		23 (46.0%)		
COMORBIDITIES								
Hypertension, N (%)	63 (66.3%)	19 (90.5%)	43 (61.4%)	25 (41.7%)	19 (54.3%)	39 (78.0%)	24 (53.3%)	MI vs elevated hsTnT only: 0.012 hsTnT >70 ng/L vs others: 0.011
Heart failure, N (%)	34 (35.8%)	13 (61.9%)	21 (30%)	44 (73.3%)	5 (14.3%)	26 (52.0%)	8 (17.8%)	MI vs elevated hsTnT only: 0.008 hsTnT >52 ng/L vs others: 0.004 hsTnT >70 ng/L vs others: 0.001
Ischemic heart disease, N (%)	21 (22.1%)	8 (38.1%)	13 (18.6%)	29 (48.3%)	2 (5.6%)	18 (36.0%)	3 (6.7%)	MI vs elevated hsTnT only: 0.079 hsTnT >52 ng/L vs others: 0.001 hsTnT >70 ng/L vs others: 0.001
Atrial fibrillation, N (%)	26 (27.4%)	3 (14.3%)	23 (32.9%)	19 (31.7%)	10 (28.6%)	14 (28.0%)	12 (26.7%)	MI vs elevated hsTnT only: 0.098
Chronic kidney disease, N (%)	20 (21.1%)	8 (38.1%)	18 (25.7%)	21 (93.3%)	39 (54.2%)	18 (78.3%)	32 (44.4%)	MI vs elevated TnT only: 0.035 hsTnT >52 ng/L vs others: 0.001 hsTnT >70 ng/L vs others: 0.008
Diabetes mellitus, N (%)	28 (29.5%)	10 (47.6%)	18 (25.7%)	18 (30.0%)	4 (11.4%)	21 (42.0%)	7 (15.6%)	MI vs elevated hsTnT only: 0.056 hsTnT >52 ng/L vs others: 0.005 hsTnT >70 ng/L vs others: 0.005
Vascular disease, N (%)	7 (9.5%)	7 (33.3%)	7 (10.0%)	24 (40.0%)	0 (0.0%)	11 (22.0%)	3 (6.7%)	MI vs elevated hsTnT only: 0.005 hsTnT >52 ng/L vs others: 0.002 hsTnT >70 ng/L vs others: 0.035
Previous heart surgery, N (%)	7 (7.4%)	5 (23.8%)	2 (2.9%)	14 (23.3%)	0 (0.0%)	6 (12.0%)	1 (2.2%)	MI vs elevated hsTnT only: 0.007

APACHE II, Acute Physiology and Chronic Health Evaluation II; SD, standard deviation; MI, myocardial ischemia; TnT, troponin T; N, number.

TABLE 3. Echocardiographic findings.

	Total (N = 95)	Myocardial ischemia (N = 21)	Elevated hsTnT only (N = 70)	hsTnT >52 ng/L (N = 60)	hsTnT ≤52 ng/L (N = 35)	hsTnT >70 ng/L (N = 50)	hsTnT ≤70 ng/L (N = 45)	p value
EF %, mean (SD)	55.0 (14.7)	45.9 (15.3)	56.9 (13.4)	51.6 (15.7)	5 (14.3%)	51.3 (15.3)	59.1 (12.8)	MI vs elevated hsTnT only: 0.002 hsTnT >52 ng/L vs others: 0.001 hsTnT >70 ng/L vs others: 0.009
EF <54 %	20 (27.0%)	15 (71.4%)	20 (26.9%)	30 (50.0%)	9 (20.0%)	26 (52.0%)	20 (27.0%)	MI vs elevated hsTnT only: 0.001 hsTnT >52 ng/L vs others: 0.001 hsTnT >70 ng/L vs others: 0.001
EF <30 %	10 (10.5%)	5 (23.8%)	5 (7.1%)	10 (16.7%)	0 (0.0%)	9 (18.0%)	1 (2.0%)	MI vs elevated hsTnT only: 0.047 hsTnT >70 ng/L vs others: 0.017
RWMA (%)	7 (9.5%)	9 (42.9%)	7 (10.0%)	14 (23.3%)	2 (5.7%)	13 (28.9%)	3 (6.7%)	MI vs elevated hsTnT only: 0.002 hsTnT >52 ng/L vs others: 0.27 hsTnT >70 ng/L vs others: 0.012

EF, ejection fraction; SD, standard deviation; RWMA, regional wall motion abnormalities; hsTnT, troponin T; MI, myocardial ischemia; N, total number.

TABLE 4. Outcome and treatment.

	Total (N = 95)	Myocardial ischemia (N = 21)	Elevated TnT only (N = 70)	TnT >52 ng/L (N = 60)	Others (N = 35)	TnT >70 ng/L (N = 50)	Others (N = 45)	p value
ICU length of stay, mean (SD)	12.6 (10.2)	13.2 (9.9)	12.2 (10.4)	12.0 (8.9)	13.5 (12.2)	12.3 (9.5)	12.8 (11.1)	MI vs elevated Tn only: 0.668
Hospital length of stay, mean (SD)	32.5 (26.4)	32.8 (28.0)	32.3 (26.5)	31.7 (26.2)	33.9 (26.9)	31.4 (26.7)	33.8 (26.2)	MI vs elevated Tn only: 0.938
ICU mortality, N (%)	9 (9.5%)	4 (19.0%)	5 (7.1%)	8 (13.3%)	1 (2.9%)	8 (16.0%)	1 (2.2%)	MI vs elevated Tn only: 0.203* TnT >70 ng/L vs others: 0.033
Hospital mortality, N (%)	25 (26.3%)	10 (47.6%)	15 (21.4%)	20 (33.3%)	5 (14.3%)	18 (36.0%)	7 (15.6%)	MI vs elevated Tn only: 0.018 TnT >52 ng/L vs others: 0.042 TnT >70 ng/L vs others: 0.024
One-year mortality, N (%)	35 (36.8%)	14 (66.7%)	21 (30.0%)	30 (50.0%)	5 (14.3%)	27 (54.0%)	8 (17.8%)	MI vs elevated Tn only: 0.002 TnT >52 ng/L vs others: 0.001 TnT >70 ng/L vs others: <0.001
Vasoactive support, N (%)	81 (85.3%)	18 (85.7%)	78 (86.7%)	51 (85.0%)	30 (85.7%)	43 (86.0%)	38 (84.4%)	MI vs elevated Tn only: 1.00
Inotropes, N (%)	23 (24.2%)	9 (42.9%)	23 (25.3%)	20 (33.3%)	3 (8.6%)	17 (34.0%)	6 (13.3%)	MI vs elevated Tn only: 0.035 TnT >52 ng/L vs others: 0.007* TnT >70 ng/L vs others: 0.019
Mechanical ventilation, N (%)	60 (63.2%)	14 (66.7%)	44 (62.9%)	36 (60.0%)	24 (68.8%)	29 (58.0%)	31 (68.9%)	MI vs elevated Tn only: 0.750

ICU, intensive care unit; MI, myocardial ischemia, TnT, troponin T; SD, standard deviation; * Fisher exact test.

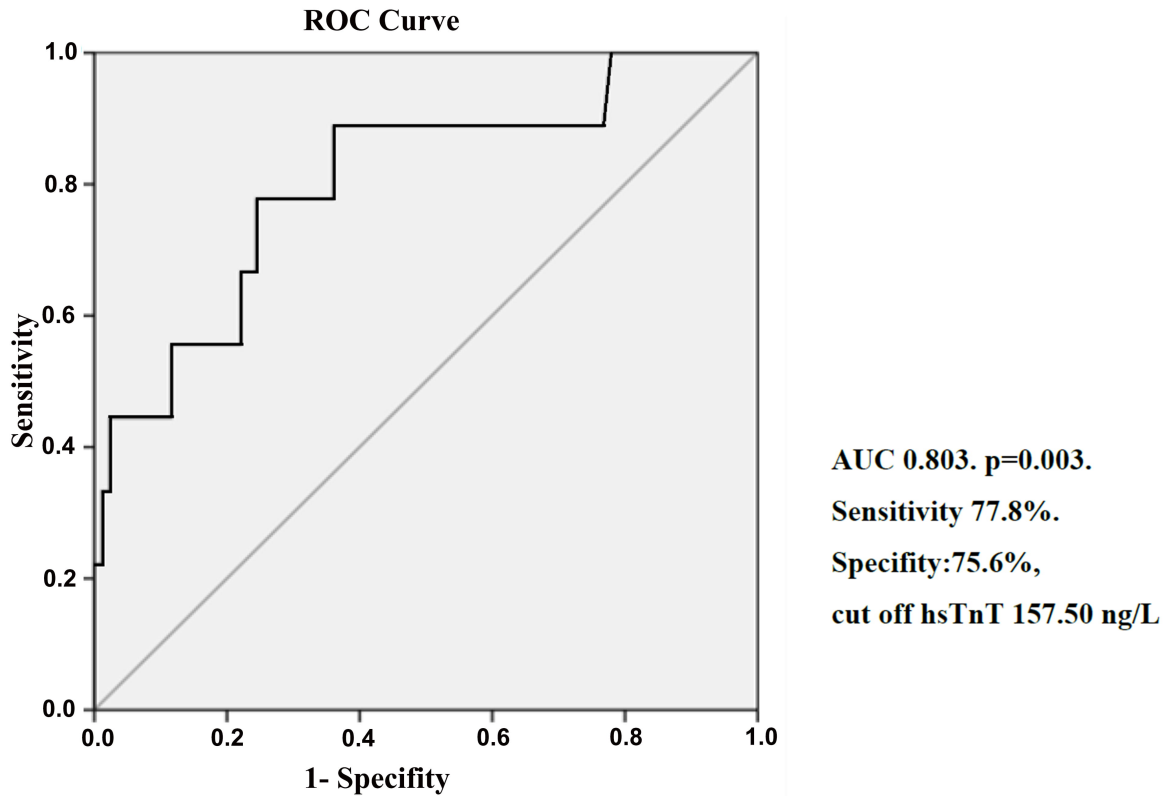


FIGURE 1. ROC curve of maximal high sensitive troponin T (hsTnT) predicting ICU-mortality.

With more widespread use of high sensitivity assays, elevated cTn levels are becoming more difficult to interpret [11, 12]. Current cTn thresholds are valid for non-critically ill patients. The universal upper reference limit lacks specificity in the ICU and the optimal troponin increase still remains to be determined and evaluated in order to avoid overestimation of ischemia [8, 18]. Troponin levels should always be interpreted in the clinical context. Differentiation between myocardial injury and ischemia can be difficult, especially in the critically ill. As mentioned, almost three-quarters of patients in our study had elevated hsTnT levels but no other signs of ischemia, reflecting a high number of patients with myocardial injury due to various pathophysiological processes in critical illness. Docherty *et al.* [18] demonstrated a rise and fall pattern of cTn levels in all critically ill patients (although with known cardiovascular risk factors) suggesting an “acute hit” mechanism of injury. Critical illness is characterised by increased sympathetic tone, which may be attributable to increased platelet aggregation and microvascular obstruction or even acute plaque rupture [20]. Peter Ammann *et al.* [21] proved that more than 70% of critically ill patients with elevated cTn levels did not have obstructive coronary disease. Critical illness could represent a stress test where non-critical coronary obstruction – previously undiagnosed, might become important [22, 23]. Many pathologies can cause an imbalance between myocardial oxygen supply and demand, which leads to ischemia [24]. This is also sometimes referred to as demand ischemia, which can be also caused by anaemia, tachycardia and suboptimal diastolic ventricular filling, hypotension or sepsis (inappropriate oxygen consumption) and many others [25, 26].

ECG changes could be non-specific in this setting [27]. We found that patients with MI had higher maximal hsTnT levels than those without clinical signs (ECG changes, RWMA, decreased LVEF, etc.). Also, inotropes were more commonly used in patients with MI, possibly suggesting more profound myocardial dysfunction. The use of vasopressors and mechanical ventilation was not, in contrast to studies by Lim and Ostermann, significantly associated with MI. In our study, previously diagnosed ischaemic heart disease was not significantly associated with MI, however, it was associated with elevated troponin levels. This may imply that myocardial ischemia in the critically ill is truly more often due to supply-demand imbalance or possible toxic effects from mediators than acute plaque rupture or other coronary occlusive events. Another possible explanation is that many patients simply did not have any diagnostics of ischemic heart disease made before ICU admission. Apart from supply-demand ischemia, both Ammann and Ostermann *et al.* [21, 28] showed that there is a significant association between elevated cTn and markers of systemic inflammation: IL-6, its soluble receptor and TNF- α . These substances could mediate myocardial depression, and they, especially TNF- α , have been implicated in increased cardiomyocyte permeability. This could explain cTn release without irreversible myocardial injury or necrosis, possibly due to transient loss of membrane integrity and release of cTn from the cytosolic pool [29–31]. Such cTn release without cell necrosis has been shown in some in vitro studies [32].

In previous studies, troponin elevations have also been described in a heterogeneous group of patients, medical and surgical, with pulmonary embolism, heart contusion, intracerebral pathology, myocarditis or renal failure. Causes for

TABLE 5. Odds ratios of Myocardial ischemia and elevated high-sensitive troponin (hsTnT) to predict inotropes use, decreased left ventricular ejection fraction (LVEF), regional wall motion abnormalities (RWMA) and mortality.

	Odds ratio (95% CI)	Statistics (<i>p</i>)
hsTnT >52 ng/L		
Inotropes use	5.33 (1.45 to 19.56)	0.016
LVEF <30%	14.76 (0.84 to 260.20)	0.064
RWMA	5.02 (1.07 to 23.60)	0.041
ICU mortality	5.23 (0.625 to 43.725)	0.120
Hospital mortality	3.00 (1.010 to 8.908)	0.048
1-year mortality	6.00 (2.051 to 17.554)	0.001
hsTnT >70 ng/L		
Inotropes use	3.35 (1.184 to 9.472)	0.022
LVEF <30%	9.65 (1.172 to 76.620)	0.035
RWMA	3.87 (1.032 to 14.533)	0.045
ICU mortality	8.38 (1.004 to 69.924)	0.050
Hospital mortality	3.05 (1.133 to 8.230)	0.027
1-year mortality	5.43 (2.1099 to 13.971)	0.005
Myocardial ischemia		
Inotropes use	1.53 (0.565 to 4.1572)	0.400
LVEF <30%	4.06 (1.048 to 15.748)	0.043
RWMA	7.71 (2.414 to 24.645)	0.001
ICU mortality	3.06 (0.740 to 12.643)	0.120
Hospital mortality	3.33 (1.190 to 9.329)	0.020
1-year mortality	4.66 (1.647 to 13.222)	0.004

the troponin elevations in these situations are multifactorial and can be sometimes difficult to interpret [11, 25, 26, 33]. Elevated troponin levels without other signs of ischemia are myocardial injuries, which can be acute or chronic, depending on the troponin dynamic [1].

Our study was novel in its emphasis on trans-thoracic echocardiographic imaging use in diagnosing myocardial ischemia. We showed an inverse correlation between hsTnT levels and LVEF. Similar conclusions were made by Ammann *et al.* [21] and ver Elst *et al.* [34] who also showed an association between troponin elevation and evidence of LV dysfunction on transoesophageal echocardiography in septic patients. Given that echocardiographic abnormalities, whether global LV dysfunction or RWMA, are associated with increased hsTnT, an echocardiographic exam should be a standard procedure in all these patients. Even though

echocardiography is difficult to perform in some patients (obese, COPD, mechanical ventilation), it remains the quickest and simplest technique to assess cardiac function in the critically ill [35].

We found that the incidence of MI was higher and ICU mortality was significantly lower in the prospective group and that maximal hsTnT in our prospective arm predicted ICU mortality. Our study was not designed (sample size was too small) to make definitive conclusions on whether systematic detection and treatment of MI could influence ICU mortality. Previous studies of Lim and Ostermann had an intriguing conclusion that there is no difference in mortality between clinically recognised and unrecognised myocardial ischemic events [4, 6]. In contrast to previous studies, our results were available to the medical team all the time, but specific therapeutic interventions upon the diagnosis of MI were applied only in half of all patients – they received antiplatelet or anti-ischemic treatment and two also underwent angiography. It remains unclear whether traditional antiplatelet, anti-ischemic or interventional treatments are appropriate or beneficial in treating MI in the ICU [3]. To date, there have been no randomised trials in this field and there are currently no guidelines regarding the management of MI in the ICU. Retrospective analyses by Poe *et al.* [36] showed that patients with high cTn levels had lower 30-day mortality if treated with beta-blockers or aspirin than those who were not. However, the potential for iatrogenic harm from treatment presents a challenge for the physician to decide on a plan of action; recent surgery or coagulation disorders may limit the use of antiplatelets, and cardiovascular instability may preclude the use of beta-blockers and nitrates [2, 3]. Moreover, in the setting of demand ischemia, it may be more appropriate to try to control physiologic variables – tachycardia, hypotension, anaemia. This could even prevent MI and improve outcome. Also, as emphasised in the Universal Definition, early cooperation with cardiologists is of great importance [2]. Our results are additionally supported by studies of post-mortem examinations on ICU patients showing that MI in the ICU is the most frequently missed diagnosis likely to impact outcome [37].

6. Study limitations

Our study had some limitations. Firstly, we conducted a single-centre study. Although our study sample was powered to detect mortality, it was not big enough for other subgroup analyses. While we had several exclusion criteria and recorded known patient comorbidities, we have not recorded smoking history, the presence of dyslipidaemia or family history for cardiovascular diseases, which could be important. We have also not recorded the use of cardioprotective medication. Although we followed our patients for up to one year, autopsy was not performed in all patients. Therefore, we do not know the exact cause of death. And, as stated in discussion, the major limitation of our study is comparison of a prospective protocol-driven approach to detect MI with retrospective analysis of a clinically driven approach.

7. Conclusions

In conclusion, high hsTnT and MI in critically ill patients are common and underdiagnosed. A methodical approach with serial troponin measurements, 12-lead (not only 2 or 3 lead) ECG and echocardiography is more successful in detecting MI compared to clinically driven decision making. Maximal hsTnT during ICU stay predicts ICU mortality. High prognostic value of elevated hsTnT and MI to predict hospital and 1-year mortality was also confirmed. Further research is necessary to better understand the various aetiologies of troponin rise in the ICU patients, to define appropriate diagnostic criteria for MI and injury in order to identify these patients and to develop an optimal treatment plan for them.

AUTHOR CONTRIBUTIONS

GK was responsible for data collection, basic statistics and wrote the manuscript; MM was responsible for data collection, echocardiography revisions, reviewing the manuscript; MG was responsible for data collection, reviewing the manuscript; GV and MP were responsible for the conception of the study, evaluation of data, reviewing the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval for this study was obtained from the National Medical Ethics Committee (Affiliation: Ministry of Health of the Republic of Slovenia; approval Number: 0120-317/2017/3) and IRB of General and Teaching Hospital Celje.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Matej Podbregar is serving as one of the Editorial Board members of this journal. We declare that Matej Podbregar had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LA.

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