

# Coronary features in septic patients with elevated cardiac troponin

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## Abstract

**Introduction:** Cardiac troponin, which is frequently elevated in septic patients, represents a diagnostic challenge in everyday clinical practice.

**Aim:** To investigate coronary features in septic patients with elevated cardiac troponin I (cTnI) and mechanisms of myocardial infarction.

**Material and methods:** A single-center retrospective observational study was conducted in consecutive cTnI-positive septic patients undergoing coronary angiography during index hospitalization.

**Results:** From January 2012 to December 2022, 74 patients with peak cTnI 16647 ng/l (normal < 40 ng/l), peak C-reactive protein 234 mg/l (normal < 5 mg/l), peak procalcitonin 14 µg/l (normal < 0.20 µg/l), arterial lactate 5.1 mmol/l (normal < 2.0 mmol/l), and positive hemocultures in 39% were enrolled. Obstructive coronary disease (> 70% diameter stenosis) was documented in 65%, with multivessel involvement in 51%. Chronic total occlusion (CTO) was present in 35%, and > 50% unprotected left main (ULM) stenosis in 22%. Definite or possible acute culprit lesions were documented in 9.5% and 6.8%, respectively. The median SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score was 16 (25th and 75th IQR 0–34). Peak cTnI was significantly elevated in patients with a definite acute culprit lesion (67,659 ng/l) compared to a possible (18,422 ng/l;  $p = 0.030$ ) or no acute culprit lesion (13,410 ng/l;  $p = 0.021$ ). Only a weak, non-linear correlation between SYNTAX score and peak cTnI was documented ( $r^2 = 0.088$ ;  $p = 0.006$ ).

**Conclusions:** Two-thirds of septic patients with elevated cTnI have obstructive coronary disease, with multivessel involvement in around 50%, significant ULM stenosis in 20%, and CTO in 40%. An acute culprit lesion, which is present in up to 10%, is associated with significantly elevated cTnI compared to patients with stable coronary disease.

**Key words:** sepsis, coronary angiography, cardiac troponin.

## Summary

Scientific evidence on coronary artery disease in sepsis is rather limited. We found that two-thirds of septic patients with elevated cardiac troponin I (cTnI) have obstructive coronary disease with complex features, including multivessel involvement in up to 50%, significant unprotected left main stenosis in up to 20%, and chronic total occlusion in up to 40%. Acute culprit lesions, which were apparent in up to 10%, were associated with markedly elevated cTnI levels. These patients may be candidates for coronary angiography, percutaneous coronary intervention, and antiplatelet treatment.

## Introduction

Elevated cardiac troponin is a well-established phenomenon in sepsis, which is characterized by dysregulated host response to infection and organ dysfunction [1, 2]. An increased systemic inflammatory response may lead to coronary plaque destabilization and rupture, fol-

lowed by obstructive thrombosis due to increased platelet activation and type 1 myocardial infarction [3, 4]. On the other hand, arterial hypotension and acute respiratory failure coupled with compensatory tachycardia may cause an imbalance between myocardial oxygen supply and demand, leading to type 2 myocardial infarction [5, 6]. Therefore, septic patients with coronary artery dis-

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ease (CAD) are at increased risk for myocardial infarction [7–9].

## Aim

In the present study, we investigated the incidence, extent, and characteristics of CAD in septic patients with elevated cardiac troponin and addressed possible mechanisms of myocardial infarction. We hypothesized that

**Table I.** Patient characteristics in patients who underwent coronary angiography during index hospital stay ( $n = 74$ )

Parameter	Results
Age [years]	70 (59–78)*
Male	54 (73%)
Body mass index [kg/m <sup>2</sup> ]	27.3 (24.9–32.9)*
Risk factors for coronary disease	
Hypertension	61 (82%)
Diabetes	41 (55%)
Dyslipidemia	33 (45%)
Smoker	8 (11%)
Known coronary disease	37 (50%)
Previous myocardial infarction	30 (41%)
Known congestive heart failure	31 (42%)
Left ventricular ejection fraction, %	30 (20–48)*
ST-elevation in 12-lead electrocardiogram	5 (6.8%)
Peripheral artery disease	31 (42%)
Chronic obstructive pulmonary disease	8 (11%)
Chronic renal failure	32 (43%)
Source of infection	
Respiratory	23 (31%)
Abdominal	11 (15%)
Heart valves	4 (5.4%)
Urinary tract	13 (18%)
Soft tissue	10 (14%)
Artificial material	7 (9.5%)
Unknown	6 (8.1%)
Positive isolates	
Gram-positive bacteria	31 (42%)
Gram-negative bacteria	30 (41%)
Fungi	5 (6.8%)
Viruses	5 (6.8%)
Positive hemocultures	29 (39%)
Laboratory value	
Peak arterial lactate [mmol/l]	5.1 (2.5–8.9)*
Peak cTnI [ng/l]	16647 (1760–63329)*
Peak WBC [ $10^9/l$ ]	19 (16–25)*
Peak CRP [mg/l]	234 (161–299)*
Peak PCT [ $\mu\text{g/l}$ ]	14 (4–27)*
SOFA score	10 (8–12)*

\*Median and 25<sup>th</sup>–75<sup>th</sup> IQR. cTnI – cardiac troponin I, CRP – C-reactive protein, PCT – procalcitonin, SOFA – Sequential Organ Failure Assessment, WBC – white blood cell count.

both type 1 and type 2 myocardial infarction may account for elevated cardiac troponin.

## Material and methods

This was a single-center retrospective, observational study which enrolled consecutive septic patients with elevated high-sensitivity cardiac troponin I (cTnI) who were admitted to the Center for Intensive Internal Medicine at the University Medical Center Ljubljana (Slovenia) and underwent coronary angiography at the discretion of the treating physician during the index hospital stay.

Clinical and laboratory data and coronary angiography recordings were collected from the institutional database and department registry of critically ill patients. Peak cTnI during the hospital stay was used. Sepsis was defined according to Sepsis-3 criteria as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Degree of organ dysfunction and circulatory/cellular metabolism abnormalities were quantified by Sequential Organ Failure Assessment (SOFA) and arterial lactate concentration. Coronary angiograms were reviewed by an experienced interventional cardiologist blinded to cTnI levels who evaluated the number of diseased vessels with obstructive stenosis ( $\geq 70\%$  diameter stenosis), presence of unprotected left main stenosis (ULM) ( $\geq 50\%$  diameter stenosis), chronic total occlusion (CTO), and an acute culprit lesion. An acute culprit lesion was defined as abrupt closure with Thrombolysis in Myocardial Infarction (TIMI) flow 0–1 or TIMI 2–3 with angiographic images suggesting thrombus or ulcerated plaque [10]. Complexity of CAD was quantitatively estimated using the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score, which was calculated for each coronary lesion with more than 50% diameter stenosis in vessels of at least 1.5 mm by the proposed website algorithm ([www.syntaxscore.com](http://www.syntaxscore.com)) [11]. The decision for percutaneous coronary intervention (PCI) was at the discretion of the interventional cardiologist and intensive care physician.

## Statistical analysis

Continuous variables are reported as median with 25<sup>th</sup> and 75<sup>th</sup> interquartile range (IQR) and categorical variables as frequencies and percentages. A scatter plot was constructed to depict the relationship between SYNTAX score and peak cTnI. Whisker plots were used to graphically depict the distribution of peak cTnI according to the presence of an acute culprit lesion. Comparisons between continuous variables were performed with Student's *t*-test or Mann-Whitney *U* test, and comparisons between categorical variables were made using the  $\chi^2$  test. Pearson correlation was used to assess the association between SYNTAX score and peak cTnI. All probability values were two-sided, and  $p < 0.05$  was considered statistically significant. Analyses were performed

with R Software Environment for Statistical Computing and Graphics (R version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria) [12]. The STROBE checklist (<http://www.annals.org/>) was used to define the content of the manuscript and guide the drafting.

## Results

Between 1<sup>st</sup> January 2012 and 7<sup>th</sup> December 2022, among 1364 consecutive patients with sepsis/septic shock, 74 had positive cTnI and coronary angiography during the index hospital stay. The patients were predominantly men (73%) with an average age of 70 years, presence of ST-elevation in 6.8%, mean left ventricular ejection fraction 30%, mean peak cTnI 16,647 ng/l (normal < 40 ng/l), and arterial lactate of 5.1 mmol/l, with values above 2 mmol/l in 81% (Table I). Although the infection source was variable, the respiratory tract was predominant (31%), and hemocultures were positive in 39%. The systemic inflammatory response was characterized by increased white blood count ( $19.0 \times 10^9/l$ ), C-reactive protein (234 mg/l; normal < 5 mg/l), and procalcitonin (14  $\mu$ g/l; normal < 0.20  $\mu$ g/l).

Intensive care treatment included intubation/mechanical ventilation (92%), norepinephrine/vasopressin (95%), dobutamine/epinephrine (74%), hemodialysis (38%), PCI (24%) and coronary artery bypass grafting (8.1%). Intensive care unit survival was 39% and hospital survival was 31%. There was no significant difference in intensive care unit survival (56% vs. 34%;  $p = 0.100$ ) or hospital survival (39% vs. 29%;  $p = 0.400$ ) between patients with or without PCI.

Obstructive coronary disease (> 70% diameter stenosis) was documented in 65%, with multivessel involvement in 51%. Chronic total occlusion (CTO) was present in 35% and > 50% unprotected left main (ULM) stenosis in 22% (Table II). Definite or possible acute culprit lesions were documented in 9.5% and 6.8%, respectively. There was only a weak, non-linear correlation between SYNTAX score and peak cTnI ( $r^2 = 0.088$ ;  $p = 0.006$ ) (Figure 1).

Peak cTnI was significantly elevated in patients with a definite acute culprit lesion (67,659 ng/l; IQR 49,426–90,153 ng/l) compared to patients with a possible (18,422 ng/l; IQR 6060–21,965 ng/l;  $p = 0.030$ ) or no acute culprit lesion (13,410 ng/l; IQR 1052–61041 ng/l;  $p = 0.021$ ) (Figure 2).

## Discussion

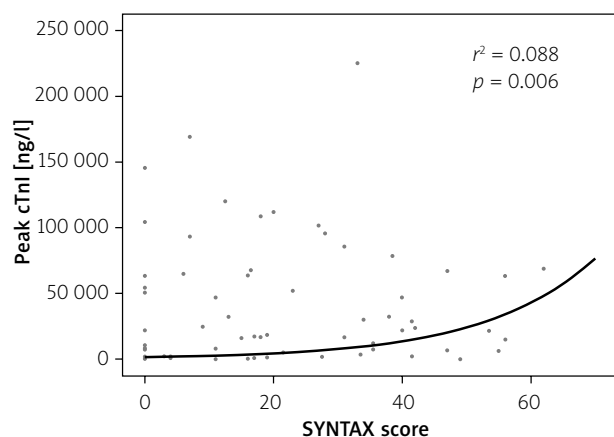
We found that two-thirds of septic patients with elevated cTnI have obstructive coronary disease with complex features, including multivessel involvement in around 50%, significant ULM stenosis in around 20%, and CTO in up to 40%. In a similar study, Tsai *et al.* [13] investigated 239 patients hospitalized for acute infection who developed acute myocardial infarction without ST-elevation and found an even higher percentage of obstructive CAD,

**Table II.** Findings on coronary angiography

Parameter	CAG during index hospitalization (n = 74)
Obstructive CAD ( $\geq 70\%$ stenosis)	48 (65%)
Extent of coronary disease	
1-vessel	13 (18%)
2-vessel	9 (12%)
3-vessel	29 (39%)
$\geq 50\%$ left main stenosis	16 (22%)
$\geq 1$ Chronic total occlusion	26 (35%)
Presence of acute culprit lesion	
Definite	7 (9.5%)
Possible	5 (6.8%)
Location of acute culprit	
Left main	1 (1.4%)
Left anterior descending artery	4 (5.4%)
Left circumflex artery	3 (4.1%)
Ramus intermedius	0 (0%)
Right coronary artery	3 (4.1%)
Saphenous vein graft	1 (1.4%)
SYNTAX score	16 (0–34)*

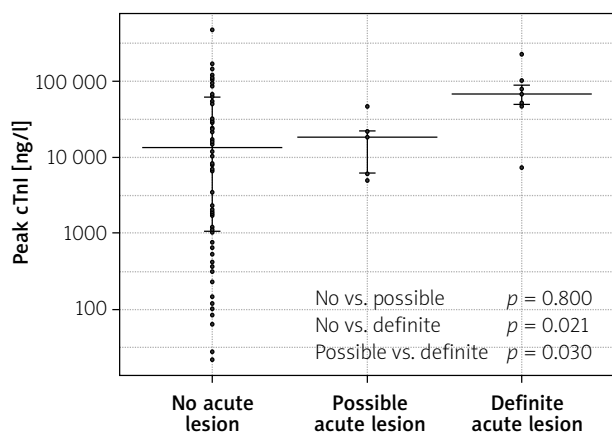
\*Median and 25<sup>th</sup>–75<sup>th</sup> IQR; SYNTAX – Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

with multivessel involvement in 95%, significant ULM in 27%, and CTO in 35%. Another study in 78 septic patients, which excluded patients with known CAD, showed obstructive CAD in only 41% [14]. In contrast to these studies, we also used the generally accepted SYNTAX score to quantitatively describe the severity of CAD [11]. Although statistically significant, the correlation between SYNTAX score and peak cTnI was very weak and clinically meaningless. This is in contrast with our hypothesis that



**Figure 1.** Relationship between SYNTAX score and peak concentration of cTnI (logarithmic scale) in patients with coronary angiography during index hospitalization

cTnI – cardiac troponin I, SYNTAX – Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.



**Figure 2.** Peak cardiac troponin I (cTnI) in patients without an obvious acute culprit lesion, with a possible acute culprit lesion, and with a definite acute culprit lesion who underwent coronary angiography during index hospital stay

increased complexity of CAD would be associated with more pronounced elevations in cTnI.

The added value of our study lies in addressing the incidence of acute culprit lesions, which were apparent in up to 10%. Despite the fact that assessment was performed by an experienced interventional cardiologist blinded to cTnI levels and was based on predefined angiographic criteria, such a classification is subjective, given the shortcomings of coronary angiography. This was also the reason for creating a subgroup of “possible acute culprit”. Intravascular imaging, especially optical coherence tomography (OCT), which would provide much more accurate plaque characterization and probably even further increase the percentage of acute culprit lesions, was not used.

While stable CAD is likely to be responsible for type 2 myocardial infarction, presence of an acute culprit lesion may result in type 1 myocardial infarction, which was characterized by much more pronounced elevation in cTnI. However, caution is warranted in making this distinction, which may be especially problematic in septic patients addressed in our study. The presence of significant stenosis and performance of PCI are not sufficient to clearly distinguish type 1 from type 2 myocardial infarction. Furthermore, septic patients often experience multifactorial myocardial injury related to cytokine-mediated myocardial damage, microvascular dysfunction, and septic cardiomyopathy, which may by itself cause or perpetuate myocardial necrosis.

In view of the rather limited scientific evidence on CAD in sepsis [13–16], we believe that our study may represent the initial step to better stratify septic patients by using cTnI. This is practically important in view of obvious difficulties in symptom reporting in sedated and mechanically ventilated patients and frequent lack of obvious ischemic changes in the 12-lead electrocardiogram. Patients with very high cTnI might be candidates

for coronary angiography, PCI, and antiplatelet treatment. On the other hand, one must consider potential interventional risks in the setting of a critical condition, multiorgan failure, and threat of bleeding, which have to be counterbalanced with potential PCI benefits. Although not designed to address potential benefits, our study did not show a significant association between PCI and either intensive care unit or hospital survival. Identification of septic patients who may benefit from PCI therefore remains a major challenge, which should be addressed in future appropriately designed and powered clinical studies. Since septic patients exhibit a broad spectrum of organ dysfunction, the SOFA score could be used for further risk stratification and to assess whether angiographic findings are predictive of survival independently of SOFA score, or conversely, if PCI may improve prognosis in specific subgroups defined by SOFA. Moreover, ROC curves for SYNTAX score, cTnI, SOFA score, and their combination could uncover eventual synergistic prognostic value, strengthen clinical relevance of the angiographic findings, and eventually improve decision-making for the invasive coronary strategy in septic patients.

## Conclusions

Our results, however, should be interpreted in view of several study limitations. This is a single-center retrospective observational study with a rather small number of patients, which precluded subgroup analyses. Because of the retrospective design of our study, we cannot provide more detailed information on ST depression suggestive of myocardial infarction. We reported only obvious ST elevation, which was rather rare. The decision for coronary angiography and PCI was not protocolized but individually decided by the treating physicians. We therefore do not know the number of septic patients with positive cTnI who did not undergo coronary angiography either because of the decision of the treating physician or because of the severe clinical condition or death before any intervention. This may represent a clinically very sick and important subgroup, introducing potential selection bias. Furthermore, data on the exact timing of coronary angiography were unavailable. Based on all these limitations, our findings need further validation in external and preferably larger cohorts of patients.

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## Ethical approval

The study was approved by the National Medical Ethics Committee (0120-377/2020/06 and 43/11/97).

## Conflict of interest

The authors declare no conflict of interest.

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