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Elevated serum amylase concentrations are associated with worse in-hospital outcomes among patients with acute myocardial infarction

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Abstract

Background In light of the well-established connection between sympathetic overactivity and early adverse events in myocardial infarction (MI) patients, this study aims to explore the potential association between serum amylase levels and in-hospital outcomes in patients with acute MI.

Methods Patients aged ≥ 18 years that were hospitalized due to acute MI were prospectively included in the present study. All patients underwent clinical and laboratory examination, transthoracic echocardiography and were referred for invasive cardiology work-up as needed. Blood sample for serum amylase measurement were obtained at the time of admission, using the spectrophotometric method. A composite outcome, comprising death, ventricular tachycardia, 3rd degree atrioventricular block, instances requiring cardiopulmonary resuscitation, and transfer for cardiac surgery, was formulated for the present analysis and was the principal outcome of interest.

Results A total of 202 patients were included in the present analysis. Patients who met the composite outcome exhibited significantly higher serum amylase levels than the counterparts who have not (55 (41–75) U/L *vs.* 87 (53–122) U/L, $p < 0.001$). Multivariate analysis revealed that amylase levels predicted the composite outcome independent of age, sex, acute MI type, serum creatinine, and cardiac troponin (adjusted odds ratio [aOR] 1.021, 95% confidence interval [CI] 1.008–1.034, $p = 0.001$). Additionally, a weak but significant association was observed between serum amylase levels and GRACE score ($r = 0.25$, $p < 0.001$).

Conclusion The findings suggest that serum amylase concentration at admission might be used as a simple, non-invasive indicator of increased sympathetic activity and adverse in-hospital outcomes in patients with acute MI.

Keywords Myocardial infarction, Amylase, Acute coronary syndrome, In-hospital mortality, Malignant arrhythmia

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Introduction

Acute myocardial infarction (MI) stands as one of the leading causes of global mortality [1]. The advent of primary percutaneous coronary intervention (pPCI) has yielded considerable advancements in terms of prognosis for patients with acute MI [2, 3]. Nevertheless, early mortality and long-term prognosis are still unsatisfactory in these patients, and the burden that cardiovascular diseases pose to global healthcare is still substantial [1, 4]. Despite the fact that a myriad of prognostic risk scores were developed, risk stratification in terms of short-term outcomes among patients with MI is still challenging [5–7].

Malignant ventricular arrhythmias are chief culprits that may impact short-term prognosis as they represent the most commonly reported cause of death in acute MI, often occurring even in the first minutes following MI [8, 9]. Previous research has indicated that increased activity of the sympathetic nervous system (SNS) is one of the important factors in the development of ventricular arrhythmias during acute ischemia [10, 11].

In line with this, amylase is a heterogeneous enzyme predominantly produced by the pancreas and salivary glands in humans [12]. Beyond its role in pancreatitis, serum amylase levels have been identified as predictors of adverse outcomes in various critical conditions, including hypovolemic shock, sepsis, cardiac surgery, and aortic dissection [13–17]. Importantly, hyperamylasemia observed in these situations cannot be solely attributed to pancreatic cell damage [13–17]. Emerging evidence instead supports the concept that salivary alpha-amylase, a specific isoform of amylase, may serve as a non-invasive surrogate marker reflecting increased activity of the sympathetic nervous system (SNS) [18, 19]. Given the well-documented sympathetic overactivity in acute MI patients and its association with poor early outcomes, this study aimed to assess whether serum amylase levels correlate with adverse in-hospital outcomes in consecutive acute MI patients admitted to a tertiary care hospital. A secondary objective was to examine potential associations between serum amylase concentrations and various clinical and laboratory parameters in this cohort.

Materials and methods

The present study was conducted at the Cardiovascular Diseases Department, University Hospital of Split, during the period from January 2019 to December 2020. The study adhered to the ethical principles outlined in the Helsinki Declaration, and the Ethics Committee of the University Hospital of Split granted approval for the study (Number: 500–03/18–01/84; Date: 31 January 2019). Before enrollment in the study, all participants received detailed information about the study procedures, and each participant provided written informed consent.

A total of 202 patients aged ≥ 18 years were consecutively enrolled in the study. The primary inclusion criterion was the diagnosis of acute MI, aligned with the contemporary guidelines outlined by the European Society of Cardiology (ESC) [20]. Patients with active malignancy, acute or chronic gastrointestinal conditions (*e.g.*, inflammatory bowel disease, pancreatic pathologies, coeliac disease), anorexia nervosa, chronic kidney disease, parotitis, chronic alcohol abuse, liver cirrhosis, prior heart failure, acute infection, and autoimmune disorders were excluded from participation in the study.

The patient follow-up extended until discharge from the hospital or fatal event. Upon admission, a comprehensive clinical assessment, including detailed medical history and physical examination, was conducted by an attending cardiologist. Body weight (kg) and height (cm) measurements were taken using a calibrated scale (Seca, Birmingham, UK). Office blood pressure was measured in all patients as per standard protocols using sphygmomanometer. Within the initial 24 h of admission, all patients underwent a transthoracic echocardiography (TTE) examination using the Vivid 9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA). Echocardiographic measurements were obtained and analyzed in accordance with the guidelines provided by the ASE for performing a comprehensive TTE examination in adults [21]. Left ventricular ejection fraction was determined following the modified Simpson's rule.

To evaluate the risk of in-hospital mortality, the Global Registry of Acute Coronary Events (GRACE) score and GRACE 2.0 were utilized [22, 23]. The updated version of the GRACE score, i.e. 2.0, employs values obtained from β of regression models using nonlinear functions, differing from previous versions, and aggregates these values to estimate the overall probability of adverse outcomes without conversion to specific points [23].

All patients requiring pPCI received treatment from a skilled interventional cardiologist with extensive procedural expertise in the certified cardiac catheterization laboratory. The preferred approach in most cases was radial rather than femoral, and patients received guideline-recommended pharmacological therapy before and after the procedure [20]. Referral decisions for cardiac surgery were made by the Heart Team, comprising both cardiac surgeons and interventional cardiologists.

Peripheral blood samples were collected upon admission and promptly processed for analysis by the same medical biochemist, blinded to the subject group allocation. All analyses were performed in a certified laboratory following the standards of good laboratory practice.

Serum amylase levels were determined using the spectrophotometric method (Beckman Coulter, Inc., Brea, CA, USA). Cardiac troponin concentrations were measured using a chemiluminescent microparticle immunoassay employing the ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Laboratories, Chicago, IL, USA). Other laboratory values, including serum lipase, were assessed following standard operating procedures. The modified shock index (MSI) was calculated by dividing heart rate by mean arterial pressure.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 28.0, Armonk, NY, USA) and GraphPad Prism for Windows (Version 8.01, La Jolla, CA, USA) was used for data presentation. Categorical variables were presented as n (%) and were analyzed using chi-squared test or Fisher's exact test. Normality of data distribution was assessed using Shapiro–Wilk test. Independent continuous variables were presented as median with 25 th and 75 th percentile or mean ± SD, and compared using Mann–Whitney test or Student's t-test, depending on data distribution. In cases with three or more groups Kruskal–Wallis test was employed. Spearman's rank correlation coefficient was used to establish correlation between variables of interest, and simple linear regression to explore an association between serum amylase concentrations and GRACE score. Multiple linear regression model was constructed to establish whether serum amylase concentrations predict GRACE score independently of sex, acute MI type and high-sensitivity Troponin I (hs-TnI) levels.

For this analysis, we formulated a composite outcome that included death, ventricular tachycardia (VT) at any point during hospitalization, 3rd degree atrioventricular (AV) block (regardless of the infarct-related artery), instances requiring cardiopulmonary resuscitation (CPR), and transfer for cardiac surgery. A patient was considered to have reached the composite outcome if at least one of its components was present. Utilizing multiple logistic regression, we assessed whether serum amylase levels serve as a predictive factor for the aforementioned composite outcome, accounting for variables such as age, sex, type of MI, serum creatinine, and hs-TnI levels. A statistical significance level of $p < 0.05$ was set for all analyses.

Results

A total of 202 consecutive patients diagnosed with acute MI were included in the present study. The composite outcome (death, malignant arrhythmia, cardiac surgery referral, CPR on admission) was reached in 32 (15.8%) patients. Patients who reached the composite outcome were older ($p = 0.006$), more commonly women ($p = 0.019$), and were more likely to be dyspneic on admission to hospital ($p = 0.036$). Furthermore, these patients had higher GRACE in-hospital mortality ($p < 0.001$), lower MAP ($p = 0.018$) and were more likely to have multivessel disease ($p = 0.024$) and more likely to receive aspirin in chronic therapy ($p = 0.031$). No significant differences between groups were found in other baseline characteristics of interest (Table 1).

Amylase serum levels were higher in patients who reached the composite outcome (55 (41–75) U/L *vs.* 87 (53–122) U/L, $p < 0.001$) (Fig. 1). Furthermore, multiple logistic regression demonstrated that serum amylase levels predict the aforementioned composite outcome irrespective of age, sex, acute MI type, serum creatinine and hs-TnI levels (aOR 1.021 (95% CI 1.008–1.034), $p = 0.001$) (Table 2).

Notably no significant difference observed in serum lipase levels between the two groups of interest (23 (15–36) U/L *vs.* (22.5 (12–40) U/L, $p = 0.570$), no distinction in serum amylase levels was evident among patients with STEMI and NSTEMI (58 (41–85) U/L vs. (56 (42–80.8) U/L, $p = 0.749$). Additionally, amylase levels did not differ with respect to the culprit artery ($p = 0.744$).

Regression analysis demonstrated that amylase serum concentrations are in positive relationship with GRACE score ($r = 0.25$, $p < 0.001$) (Fig. 2). The association between amylase and GRACE score remained significant even after adjustment for sex, acute MI type and hs-TnI levels (β ± SE, 0.19 ± 0.07, $p = 0.011$).

Weak correlations were noted between amylase and creatinine serum concentrations ($r = 0.243$, $p < 0.001$), and between amylase and hs-TnI serum concentrations ($r = -0.190$, $p = 0.007$). Accordingly, serum amylase/creatinine ratio predicted the composite outcome better than serum amylase itself (aOR 3.675 (95% CI 1.498–9.021), $p < 0.001$). On the other hand, a moderate correlation was observed between serum amylase and lipase levels ($r = 0.439$, $p < 0.001$). No correlation was found between serum lipase levels and GRACE score ($r = -0.025$, $p = 0.730$). Finally, no association was observed between serum amylase concentrations and modified shock index ($r = -0.041$, $p = 0.565$) or LVEF ($r = 0.115$; $p = 0.136$). Correlations between serum amylase levels and various clinical and laboratory variables of interest are summarized in Table 3. Although weak negative correlation was noted between serum amylase levels and hs-TnI ($r = -0.190$), the association was lost after adjustment for the possible confounders (age, sex and MI type) ($p = 0.061$).

Table 1 Comparison of baseline characteristics with respect to the composite outcome

Parameters	Total population ($n=202$)	Did not reach composite outcome ($n=170$)	Reached composite outcome ($n=32$)	*p*-value*
Age, years	65.0 ± 12.3	64.0 ± 12.1	70.6 ± 11.7	**0.006**
Male sex, n (%)	137 (67.8)	121 (71.2)	16 (50)	**0.019**
Smoking, n (%)	81 (40.1)	70 (41.2)	11 (34.4)	0.473
DM, n (%)	44 (21.8)	35 (20.6)	9 (28.1)	0.345
Hypertension, n (%)	116 (57.4)	95 (55.9)	21 (65.6)	0.308
AF, n (%)	22 (10.9)	16 (9.4)	6 (18.8)	0.121
Previous MI, n (%)	33 (16.3)	29 (17.1)	4 (12.5)	0.523
STEMI, n (%)	119 (58.9)	102 (60)	17 (53.1)	0.470
Emergent PCI, n (%)	141 (69.8)	116 (68.2)	25 (78.1)	0.265
Multi-vessel disease, n (%)	45 (22.3)	33 (19.4)	12 (37.5)	**0.024**
LVEF, %	55.0 ± 11.6	55.7 ± 11.0	50.1 ± 14.7	0.105
LVEF < 50%, n (%)	48 (23.8)	42 (24.7)	6 (18.8)	0.617
Dyspnea, n (%)	52 (25.7)	39 (22.9)	13 (40.6)	**0.036**
GRACE in-hospital mortality, %	2.0 (1.0–4.1)	1.8 (1.0–3.2)	4.9 (1.6–9.2)	**< 0.001**
MSI	0.83 (0.65–1.06)	0.80 (0.63–1.04)	0.90 (0.71–1.15)	0.065
MAP, mmHg	100 (87–110)	100 (90–110)	92 (70–99)	**0.018**
hs-TnI, ng/L	320 (65–3761)	366 (70–3761)	292 (53–3476)	0.564
Serum creatinine, µmol/L	98.0 ± 77.9	96.2 ± 80.8	107.7 ± 61.0	0.361
Glucose, mmol/L	7.7 (6.1–10.3)	7.6 (6.0–9.9)	9.0 (6.6–10.9)	0.088
ASA, n (%)	36 (17.8)	26 (15.3)	10 (31.2)	**0.031**
BB, n (%)	51 (25.2)	41 (24.1)	10 (31.2)	0.395
CCB, n (%)	26 (12.9)	20 (11.8)	6 (18.8)	0.280
ACEi, n (%)	66 (32.7)	53 (31.2)	13 (40.6)	0.297
Hypoglycemics, n (%)	41 (20.3)	34 (20.0)	7 (21.9)	0.809
Infarct-related artery, n (%)				
RCA	55 (27.2)	45 (26.5)	11 (34.4)	0.323
LAD	74 (36.6)	68 (40.0)	6 (18.8)	0.022
LCx	21 (10.4)	20 (11.8)	1 (3.1)	0.143
OM1	4 (2.0)	4 (2.4)	0 (0.0)	0.382
Diagonal branch	3 (1.5)	1 (0.6)	2 (6.3)	0.015
Multivessel disease	45 (22.3)	33 (19.4)	12 (37.5)	0.024
Composite outcome components, n (%)				
Death	5 (2.5)	N/A	5 (15.6)	N/A
CPR on admission	5 (2.5)	N/A	5 (15.6)	N/A
Ventricular tachycardia	10 (5.0)	N/A	10 (31.3)	N/A
3rd degree AV block	8 (4.0)	N/A	8 (25)	N/A
Cardiac surgery transfer	11 (5.4)	N/A	11 (34.3)	N/A

Data are presented as mean ± standard deviation, n (%) or median (interquartile range)

Abbreviations: ACEi angiotensin converting enzyme inhibitors, *AF* atrial fibrillation, *ASA* acetylsalicylic acid, *AV* atrioventricular, *BB* beta-blockers, *CCB* calcium channel blockers, *CPR* cardiopulmonary resuscitation, *DM* diabetes mellitus, *hs-TnI* high-sensitivity troponin I, *LAD* left anterior descending, *LCx* left circumflex artery, *LVEF* left ventricular ejection fraction, *MAP* mean arterial pressure, *MI* myocardial infarction, *MSI* modified shock index, *OM1* obtuse marginal branch, *PCI* percutaneous coronary intervention, *RCA* Right coronary artery, STEMI ST-elevation myocardial infarction

Bold font denotes statistical significance. **p*-value is derived from the Welch's t-test, Mann–Whitney U test, Chi-squared test or Fisher's exact test, as appropriate

Discussion

To the best of our knowledge, this is the first study in which association between serum amylase levels at admission and in-hospital outcomes of patients with acute MI was explored. Findings of the study indicate that elevated serum amylase levels are notably present in patients experiencing adverse in-hospital outcomes, regardless of age, sex, type of MI, serum creatinine, and hs-TnI levels. Accordingly, an association between

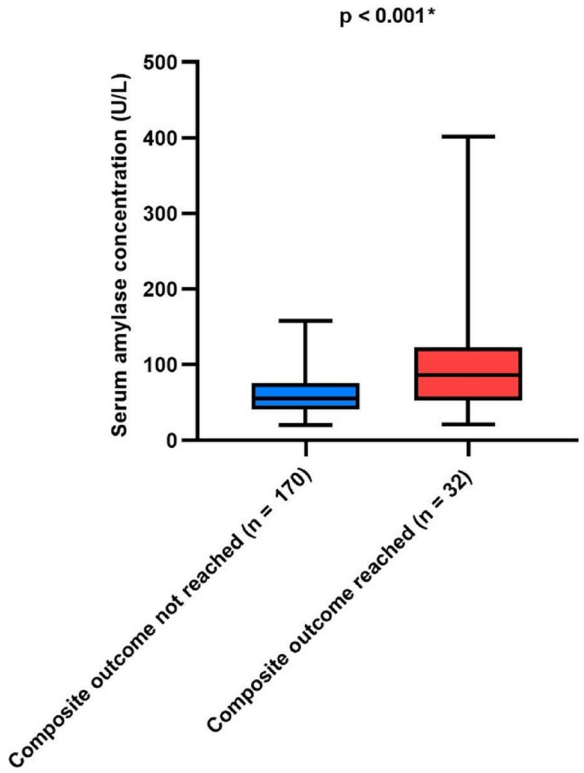

Fig. 1 Comparison of serum amylase concentration with respect to the composite outcome occurrence. *Mann–Whitney U test

Table 2 Multiple logistic regression analysis of the independent predictors of the composite outcome

Parameters	β	SE	aOR (95%CI)	*p*-value
Age, years	0.029	0.019	1.029 (0.992–1.068)	0.123
Sex[a]	− 0.533	0.450	0.587 (0.243–1.418)	0.236
MI type[b]	− 0.325	0.429	0.723 (0.312–1.674)	0.449
Amylase, IU/L	0.021	0.006	1.021 (1.008–1.034)	**0.001**
Serum creatinine, µmol/L	− 0.001	0.003	0.999 (0.993–1.004)	0.627
hs-TnI, ng/L	0.000	0.000	1.000 (1.000–1.000)	0.424

Bold font denotes statistical significance

Abbreviations: hs-TnI high-sensitivity troponin I, *MI* myocardial infarction, *STEMI* ST-elevation myocardial infarction

[a] Reference group are male subjects [b]Reference group are STEMI patients

GRACE score, a well-recognized prognostic score in MI, and serum amylase concentrations was established.

Several explanations may account for the elevated serum amylase levels observed in patients with poorer in-hospital outcomes. Extensive evidence suggests that sympathetic hyperactivity plays a critical role in the context of acute MI [24, 25]. Excessive SNS activity has been associated with unfavorable post-MI outcomes, while early beta-blocker administration has shown a

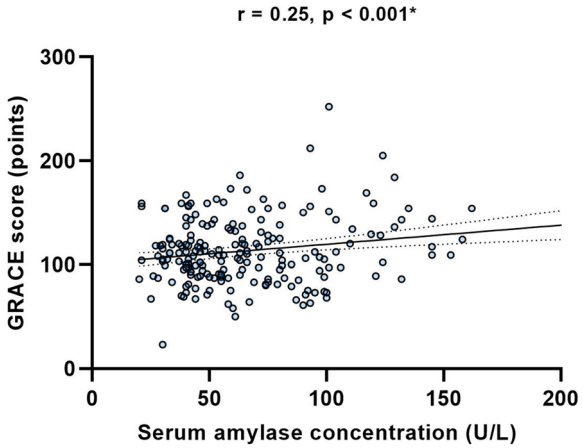

Fig. 2 An association between serum amylase concentrations and GRACE score. *Simple linear regression

Table 3 Correlations between serum amylase levels and clinical and laboratory variables of interest in patients with acute myocardial infarction

Parameter	r-correlation coefficient[a]	*p*-value
Serum creatinine, µmol/L	0.243	**< 0.001**
hs-TnI, ng/L	− 0.190	**0.007**
MSI	− 0.041	0.565
MAP, mmHg	0.005	0.947
LVEF, %	0.115	0.136
Serum sodium, mmol/L	0.059	0.401
Glucose, mmol/L	0.086	0.235
Serum LDH, U/L	− 0.071	0.324
WBC	− 0.065	0.361
Serum lipase, U/L	0.439	**< 0.001**

Bold font denotes statistical significance

Abbreviations: hs-TnI high-sensitivity troponin I, *LDH* lactate dehydrogenase, *LVEF* left ventricular ejection fraction, *MAP* mean arterial pressure, *MSI* modified shock index, *WBC* white blood cells

[a] Spearman's rank correlation coefficient

positive impact by addressing the SNS disturbance as a key pathophysiological factor in this scenario [9, 26]. The mechanisms underlying sympathetic overactivity in MI are multifaceted [27–30]. Sympathetic neural reflexes can be triggered by mechanical or chemical signals originating from the infarcted myocardium or other locations, such as the atria, pulmonary receptors, carotid sinuses, and aortic arch baroreceptors [27–30]. Additionally, ischemia leads to a significant accumulation of noradrenaline in the heart through non-exocytotic mechanisms [27]. In cases of extensive MI, impaired ventricular function and the onset of acute heart failure may further exacerbate SNS activity [31].

Other contributing factors include pain and emotional stress, both recognized as potent activators of the SNS [32]. Importantly, SNS hyperactivity alters myocardial electrophysiology by elevating the resting membrane potential, enhancing abnormal automaticity, shortening ventricular action potential duration, inducing delayed afterdepolarizations at high heart rates, altering refractory periods in cardiomyocytes, and prompting long-term structural myocardial changes [33–37]. These alterations significantly heighten the risk of ventricular arrhythmias, which are pivotal drivers of adverse outcomes in MI patients [24, 25].

Stimulation of β-adrenergic receptors by norepinephrine, released from sympathetic nerve terminals, increases the production of multiple proteins, including amylase [38, 39]. In fact, salivary alpha-amylase (sAA) has been established as an indicator of acute stress triggered by diverse physiological and psychological stimuli, showing correlations with cardiovascular sympathetic activation markers, suggesting its potential utility as a simple, non-invasive surrogate marker for sympathoadrenal activity [40]. Previous research has demonstrated elevated sAA levels in patients with MI [41]. Specifically, among patients admitted with non-traumatic chest pain, patients with MI were shown to have higher sAA levels than those with alternate discharge diagnosis [41]. In contrast to our findings, the aforementioned study observed a notably higher expression of sAA concentration within the subgroup diagnosed with STEMI and anterior infarction. Importantly, since patients with non-ischemic chest pain in the above-noted study had much lower sAA, pain-induced SNS hyperactivity is probably not a major mediator of amylase secretion in acute MI.

Independent association with GRACE score further substantiates the role of amylase in prediction of outcomes in MI. Specifically, prior studies have shown that the discriminative capacity of the GRACE score exceeds that of other risk scores for acute coronary syndromes (ACS) [42]. In fact, the score can be used to tailor invasive treatment approach in patients with NSTEMI as per the latest ACS guidelines [20]. Unsurprisingly, a positive correlation between lipase and amylase levels was observed. However, lack of association between lipase levels, and both outcomes and GRACE score indicates that pancreatic injury probably wasn't a relevant contributor to increased amylase levels. Based on abundant evidence linking amylase to sympathetic activity, the association between sympathetic activity and adverse outcomes in MI patients, as well as our findings, we postulated that serum amylase concentrations might be used as a simple, non-invasive indicator of increased sympathetic activity and adverse in-hospital outcomes in patients with acute MI.

Alternatively, considering the observed correlation with creatinine, and the superior performance of the prediction model integrating creatinine compared to the one solely reliant on amylase levels, it's plausible that the link between serum amylase levels and adverse outcomes might reflect compromised kidney function, at least to some extent. For instance, hyperamylasemia is a common finding in patients undergoing cardiac surgery, and data suggests that this can largely be attributed to post-procedural impaired kidney function [16, 43]. In line with this, prior studies have consistently shown a negative association between serum amylase levels and glomerular filtration rate [13]. Finally, in extensive infarctions that lead to cardiogenic shock, hypoperfusion of the gastrointestinal system may additionally raise amylase levels [44]. These extensive infarctions often relate to significantly worse outcomes, potentially clarifying the elevated amylase levels observed in patients experiencing poorer prognoses.

There are several limitations to consider in this study. Although from perspective of outcome prediction single point measurement at admission is the goal, measurement at multiple points would provide more comprehensive insight, and perhaps indicate more adequate timing for serum amylase sampling. The single-center design and limited sample size restrict the generalizability of the results to broader populations. In line with this, longer follow-up would bring valuable information in terms of clinical relevance of our findings. Standard blood amylase testing typically reflects the total amylase activity present in the bloodstream, encompassing both pancreatic and non-pancreatic origins. In addition, amylase secretion may be influenced by certain factors which are hard to account for, such as exercise, food and alcohol consumption, smoking… Although salivary amylase contributes to the total amylase activity in the blood, it's important to note that blood amylase levels primarily represent a combination of pancreatic and extrapancreatic sources rather than specifically reflecting saliva production. Thus, the study would benefit from concomitant measurement of sAA. Finally, the interpretation is limited by the absence of data regarding serum levels of natriuretic peptides and hsCRP.

Conclusion

In summary, serum amylase levels appear to be independently linked with adverse in-hospital outcomes in patients with acute MI. The precise mechanism leading to the observed increase remains uncertain. However, it is suggested that factors such as hyperactivation of the SNS, tissue damage in organs beyond the pancreas, and impaired kidney function could potentially contribute to this elevation. Thus, preliminary evidence indicates that serum amylase concentrations could serve as a proxy for sympathetic

overactivity and concomitant increase in risk of in-hospital events in patients with acute MI. However, further research is necessary to fully understand the clinical significance and the precise role of amylase as a biomarker of SNS overactivity and prognosis in these cases.

Abbreviations

LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MSI	Modified shock index
NSTEMI	Non-ST-elevation myocardial infarction
SNS	Sympathetic nervous system
STEMI	ST-elevation myocardial infarction
WBC	White blood cells

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Authors' contributions
MM participated in conceptualization, methodology, investigation, formal analysis and original draft preparation. MK participated in visualization, investigation, formal analysis and original draft preparation. IRV participated in investigation, formal analysis and original draft preparation. DG participated in investigation, formal analysis and original draft preparation. TTK participated in investigation, formal analysis and reviewing and editing of the manuscript. JB participated in investigation, formal analysis and reviewing and editing of the manuscript. JAB participated in conceptualization, funding acquisition, project administration and reviewing and editing of the manuscript. All authors approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical Committee of the University Hospital of Split has approved this study (Number: 500–03/18–01/84; Date: 31 January 2019). Informed consent was waived for the present study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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