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Detectable troponin below the 99th percentile predicts survival in patients undergoing coronary angiography

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ABSTRACT

Background: Cardiac troponin I (cTnI) above the 99th percentile is associated with an increased risk of major adverse events. Patients with detectable cTnI below the 99th percentile are a heterogeneous group with a less well-defined risk profile. The purpose of this study is to investigate the prognostic relevance of detectable cTnI below the 99th percentile in patients undergoing coronary angiography.
Methods: The study included 14,776 consecutive patients (mean age of 65.4 ± 12.7 years, 71.3 % male) from the Essen Coronary Artery Disease (ECAD) registry. Patients with cTnI levels above the 99th percentile and patients with ST-segment elevation acute myocardial infarction were excluded. All-cause mortality was defined as the primary endpoint.
Results: Detectable cTnI below the 99th percentile was present in 2811 (19.0 %) patients, while 11,965 (81.0 %) patients were below detection limit of the employed assay. The mean follow-up was 4.25 ± 3.76 years. All-cause mortality was 20.8 % for patients with detectable cTnI below the 99th percentile and 15.0 % for those without detectable cTnI. In a multivariable Cox regression analysis, detectable cTnI was independently associated with all-cause mortality with a hazard ratio of 1.60 (95 % CI 1.45–1.76; $p < 0.001$). There was a stepwise relationship with increasing all-cause mortality and tertiles of detectable cTnI levels with hazard ratios of 1.63 (95 % CI 1.39–1.90) for the first tertile to 2.02 (95 % CI 1.74–2.35) for the third tertile.
Conclusions: Detectable cTnI below the 99th percentile is an independent predictor of mortality in patients undergoing coronary angiography with the risk of death growing progressively with increasing troponin levels.

1. Introduction

Cardiac troponin (cTn) is a cornerstone of the initial diagnostic work-up in patients with suspected cardiovascular (CV) disease, including acute myocardial infarction (AMI). Elevated cTn above the 99th percentile indicates myocardial injury. AMI is defined as the presence of acute myocardial injury and symptoms or signs of acute myocardial ischaemia according to the *Fourth Universal Definition of Myocardial Infarction* [1]. In addition to the assessment of suspected acute coronary syndrome, cTn has been associated with the presence and prognosis of

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various other CV and non-CV diseases, including myocarditis, outcome after coronary artery bypass grafting, heart failure, septic shock, coronavirus disease 2019, and cancer therapy-related cardiotoxicity [2–8].

The relevance of cTn for risk stratification in the general population has been assessed in several studies [9–11]. In an analysis of ten general population cohorts including 74,738 patients, cTn was independently associated with all-cause mortality, presence of CV disease, CV mortality and improved the prognostic value of the well-known 'European Society of Cardiology (ESC) SCORE' risk score [9]. A profound association of absolute cTn values with a subsequent increased risk was still present with detectable cTn values below the 99th percentile of the upper reference limit. The impact of cTn has also been investigated in different clinical settings in the absence of AMI [12–14]. Patients with elevated cTn above the 99th percentile had an increased risk of major CV adverse events [13]. High-sensitive cTn was associated with presence of CAD and CV death in patients with symptoms suggestive of stable angina undergoing coronary angiography [15]. Independent of AMI, detectable cTn below the 99th percentile remained associated with increased mortality, AMI, and hospitalisation for heart failure, and showed a high predictive value in proposed scoring systems [12,16,17].

Due to its cardiac specificity, response to intervention and risk factor optimisation, paralleled by its technical simplicity and cost-effectiveness, cTn is considered a high-potential biomarker for future CV risk stratification that may suggest lifestyle interventions and drug therapy in the high-risk setting [10]. Since new assays have improved sensitivity, this results in a higher frequency of troponin detection below the 99th percentile, the value of which is poorly defined [18]. Any detectable presence of cTn has the potential to improve diagnostic accuracy, allow for earlier intervention, and ultimately improve patient outcomes. However, the heterogeneity of the patient population and our limited understanding of the underlying disease mechanisms make the clinical management challenging, ultimately leading to suboptimal treatment [19].

The available evidence suggests that detectable cTn indicates CV stress thereby increasing the risk of adverse outcomes, independently of the presence of AMI. We sought to determine the prognostic implications of a detectable admission cTnI below the 99th percentile compared with no detectable cTnI in patients with suspected CV disease.

2. Methods

2.1. Study sample

The present analysis is based on the cohort of the Essen Coronary Artery Disease (ECAD) registry, including patients $\geq$ 18 years of age who were hospitalised at the West German Heart and Vascular Center, Essen, Germany, between 2004 and 2019. Details on the study have been previously reported [20]. The ECAD registry includes data from 40,461 coronary angiographies. For the present analysis, patients with no detectable admission cTnI and detectable admission cTnI below the 99th percentile of the upper reference limit were included. Patients with ST-segment elevation AMI (STEMI), patients with missing data of admission cTnI, and patients with missing follow-up information were excluded. The study was approved by the local ethics committee (19–8956-BO) and has been performed in accordance with the 1964 Declaration of Helskinki and its later amendments. After applying the exclusion criteria, 14,776 patients were included in the analysis.

2.2. Clinical characteristics and covariate assessment

Information on traditional CV risk factors from the same hospital stay was automatically retrieved from the hospital information system and merged into the database. Laboratory variables were assessed using standardised enzymatic methods (low- and high-density lipoprotein cholesterol (LDL, HDL), lipoprotein (a), creatinine). Diabetes was defined as haemoglobin A1c $\geq$ 6.5 %. Self-reported information on current smoking status and family history of premature CAD were classified as present, absent, or unknown. In addition, medication information at the time of admission was assessed (beta blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, Ca^{2+} channel blockers, diuretics, acetylsalicylic acid (ASA), P2Y12 inhibitors, oral anticoagulation, statins, other).

2.3. Assessment of cTnI

Troponin was determined by the Siemens Dimension Troponin I (detectable limit: 40 ng/L, 99th percentile: 70 ng/L until 11th August 2014) or the Siemens ADVIA Centaur contemporary high-sensitive Troponin I Ultra (detectable limit: 6 ng/L, 99th percentile: 40 ng/L; since 12th August 2014) assay.

2.4. Endpoint definition

All-cause mortality was defined as the primary endpoint. Information on survival status was obtained from all available hospital records (including partner healthcare facilities) and insurance information. Any outpatient or inpatient presentation to the West German Heart and Vascular Center, University Hospital Essen, or any partner healthcare facility after the coronary angiography was used to confirm survival status. Patients without confirmed death but no return to the healthcare provider were considered as missing follow-up.

2.5. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) if normally distributed and as median (interquartile range) if non-normally distributed. Discrete variables are reported as absolute numbers and frequencies. Continuous variables were compared using the 2-sided *t*-test or Wilcoxon test (for non-normally distributed variables). Discrete variables were compared using the Chi-square test. Cox regression analysis was used to determine the association of detectable cTnI with all-cause mortality in unadjusted and risk factor adjusted (multivariable) models. Variables adjusted for in each multivariable model included age, sex, systolic blood pressure, LDL-cholesterol, diabetes, smoking status, and family history of premature CAD. Age- and sex-adjusted subgroup analysis was conducted by stratifying for the individual main diagnosis of the respective presentation according to hospital records.

Kaplan-Meier curves illustrate the all-cause mortality stratified by the presence of a detectable cTnI below the 99th percentile with differences between groups being evaluated using the log-rank test. Subgroup analyses were performed, stratifying by age group ($<$vs. $\geq$ 65 years), sex, by previous or known cardiac or non-cardiac disease, and blood pressure (systolic blood pressure $<$ vs. $\geq$ 140 mmHg and/or diastolic blood pressure $<$ vs. $\geq$ 90 mmHg and/or antihypertensive therapy), and renal function (creatinine $<$ vs. $\geq$ 1.3 mg/dl) in univariate analysis. In patients with detectable cTnI below the 99th percentile threshold, the primary endpoint was assessed after stratification for tertiles of admission cTnI levels.

Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA). A p-value of $<$0.05 indicated statistical significance. Figures were created using Microsoft PowerPoint 365 (Microsoft Corporation, Redmond, Washington, USA), SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) and Graphpad Prism 9 (Graphad Software, San Diego, California, USA). Data are available upon reasonable request to the principal investigators of the study.

3. Results

3.1. Inclusion of patients

From 14,776 patients included in the present analysis (mean age 65.4 ± 12.7 years, 71.3 % male), 2811 (19.0 %) patients had a detectable admission troponin below the 99th percentile and 11,965 (81.0 %) patients had no detectable troponin. The Siemens Dimension Troponin I assay was used in 13,981 (94.6 %) of patients and the Siemens ADVIA Centaur high-sensitive Troponin I Ultra assay was used in 795 (5.4 %) of patients.

Patients with detectable cTnI below the 99th percentile were older without a significant difference in gender distribution. The assessment of further cardiac enzymes showed similar levels of CK, higher myoglobin (66 (48–98) vs. 53 (41–71) ng/ml; $p < 0.001$) and higher admission BNP levels (161 (50–426) vs. 61 (26–147) pg/ml; $p < 0.001$) in patients with detectable cTnI compared to those without. The assessment of medication at discharge determined a lower intake of ASA but higher rates of oral anticoagulation. Details of baseline characteristics are shown in Table 1.

Patients were stratified according to the main diagnosis of the respective presentation according to hospital records. CAD was the most frequent main diagnosis recorded in 49 % of patients, followed by valvular heart disease in 11 % of patients and heart failure in 6 % of patients (Fig. 1).

3.2. Primary endpoint analysis

There were 2379 (16.1 %) deaths from any cause during the mean follow-up of 4.25 ± 3.76 years. All-cause mortality was higher in patients with detectable cTnI below the 99th percentile compared with those without detectable cTnI (584/2811 (20.8 %) vs. 1795/11.965 (15.0 %) patients,

$p < 0.001$; Fig. 2). In univariate Cox regression analysis, detectable troponin below the 99th percentile was associated with a 78 % increase in the risk of death during follow-up. Adjusting for cardiovascular risk factors confirmed the independent effect of detectable troponin levels with unfavourable survival. Renal function is an independent determinant of cTnI levels in patients with chronic kidney disease, with an inverse correlation between glomerular filtration rate and cTnI levels [21]. To account for a potential interaction of elevated creatinine with the observed effects, creatinine levels < vs. ≥ 1.3 mg/dl were included in the multivariable analysis. This had only a slight effect on the association of detectable troponins below the 99th percentile with incident mortality (Table 2).

In the subgroup analysis, the effect of cTnI was independent from age (<vs. ≥ 65 years), sex and previously known CAD. There were no significant differences associated with the presence or absence of common CV risk factors or increased creatinine. The effect was stronger in patients with a positive family history of CAD compared with those without (Fig. 3). Also, a significant effect was recapitulated after stratifying for individual main diagnoses (Table 3).

To test whether cTnI levels in patients with detectable troponin below the 99th percentile affected the risk of all-cause mortality, patients were stratified into tertiles of cTnI levels with tertile 1 representing the lowest cTnI levels and tertile 3 representing the highest cTnI levels of the employed assay. The analysis revealed a stepwise association with increasing risk of death from tertile 1 (HR 1.63 95 % CI 1.39–1.90) to tertile 3 (HR 2.02; 95 % CI 1,74–2.35; Fig. 4).

4. Discussion

This study evaluated the predictive value of a detectable cTn below the 99th percentile in patients with suspected CV disease undergoing coronary angiography. The main findings are: (i) Detectable cTnI below the 99th percentile is a common finding in this patient population. (ii)

Table 1
Baseline characteristics. The table shows parameters assessed at initial presentation. Values are presented as number and percent of all analysed. Statistical assessment was performed using the Chi^2 test. ACEi, angiotensine converting enzyme inhibitor; ARB, angiotensin receptor blockers; ASA, acetyl salicylic acid; BNP, brain natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CRP, c-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein (a); no., number; p., percentile; yr, year old. Continuous variables are depicted as mean ± SD or median (Q1-Q3) if not normally distributed.

Characteristic	All patients (N = 14.776)	Detectable troponin < 99th p. (N = 2811)	No detectable troponin (N = 11.965)	p-value
Age (years)	65.35 ± 12.74	67.66 ± 12.60	64.80 ± 12.71	**<0.001**
Male gender – no. (%)	10,513 (71.2)	1984 (70.7)	8529 (71.4)	0.462
Cardiovascular risk factors				
Arterial hypertension	6984 (86.3)	1482 (87.7)	5502 (85.9)	**<0.001**
Systolic BP (mmHg)	137.1 ± 22.02	137.2 ± 23.55	137.1 ± 21.63	0.878
Smoking (current) – no. (%)	1539 (16.4)	293 (15.2)	1246 (16.7)	0.114
Smoking (former) – no. (%)	2442 (26.0)	441 (22.9)	2001 (26.8)	**0.001**
Smoking (any) – no. (%)	3981 (42.4)	734 (38.1)	3247 (43.6)	**<0.001**
Diabetes – no. (%)	2076 (23.8)	355 (27.8)	1721 (23.1)	0.094
Hyperlipidemia – no. (%)	4309 (55.0)	880 (53.2)	3429 (55.5)	**<0.001**
Family history of CAD – no. (%)	2568 (27.4)	395 (20.6)	2173 (29.2)	**<0.001**
Laboratory parameters				
Hemoglobin (g/dl)	13.51 ± 1.76	13.20 ± 1.92	13.59 ± 1.71	**<0.001**
CRP (mg/dl)	0.6 (0.2–1.4)	0.9 (0.5–2.0)	0.6 (0.1–1.3)	**<0.001**
Creatinine (mg/dl)	1.17 (1.02–1.37)	1.22 (1.05–1.51)	1.16 (1.02–1.34)	**<0.001**
Creatine kinase (U/l)	88 (61–132)	88 (59–137)	88 (62–131)	0.940
Myoglobin (ng/ml)	56 (42–76)	66 (48–98)	53 (41–71)	**<0.001**
LDL (mg/dl)	99 (78–126)	101 (77–127)	99 (78–126)	0.906
HDL (mg/dl)	47 (39–57)	45 (37–57)	47 (39–57)	**0.001**
LP(a) (mg/dl)	14 (6–51)	13 (6–45)	14 (6–52)	0.140
BNP (pg/ml)	73 (29–179)	161 (50–426)	61 (26–147)	**<0.001**
Medication				
ASA – no. (%)	6121 (82.4)	1223 (78.2)	4898 (83.5)	**<0.001**
P2Y12 inhibitor – no. (%)	3799 (51.7)	806 (52.3)	2993 (51.5)	0.594
oral anticoagulation – no. (%)	1417 (19.2)	404 (26.0)	1013 (17.4)	**<0.001**
Beta blocker – no. (%)	6715 (86.7)	1397 (85.7)	5318 (87.0)	0.156
Diuretic – no. (%)	5161 (66.8)	1150 (70.5)	4011 (65.8)	**<0.001**
ACEi/ARB – no. (%)	5529 (71.7)	1146 (70.4)	4383 (72.0)	0.219
Calcium channel blocker – no. (%)	2259 (29.4)	494 (30.5)	1765 (29.1)	0.275
Other antihypertensive drugs – no. (%)	1318 (17.1)	324 (20.0)	994 (16.4)	**0.001**
Statins – no. (%)	3644 (74.8)	763 (70.3)	2881 (76.1)	**<0.001**
Other lipid lowering drugs – no. (%)	198 (4.1)	45 (4.1)	153 (4.0)	0.888

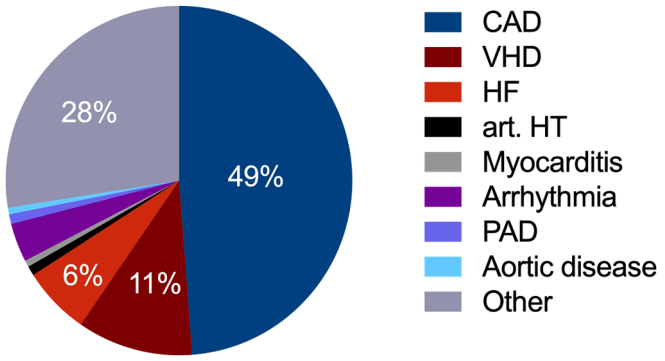

Fig. 1. Cardiovascular lead diagnosis. The pie chart delineates the frequency of lead diagnoses referring to the respective admission of included patients, as derived from the ECAD database. Art. HT, arterial hypertension; CAD, coronary artery disease; HF, heart failure; PAD, peripheral artery disease; VHD, valvular heart disease.

Patients with detectable troponin below the 99th percentile have an increased risk of all-cause mortality compared with those without detectable cTnI. (iii) There is a stepwise association with increasing all-cause mortality between tertiles of cTnI levels.

cTn is a part of the myocardial contractile apparatus and is expressed almost exclusively in the heart. Increased cTnI indicates cardiomyocyte injury, regardless of the underlying mechanism [1]. In addition to AMI, a variety of cardiac and systemic stressors can induce an increase of serum cTnI. CV causes include heart failure, arrhythmia, hypertension or hypotension, pericarditis and myocarditis, acute pulmonary embolism, periprocedural cTn elevation, Takotsubo syndrome and cardiac contusion. Anaemia, infection, pulmonary disease and renal disease are the most common systemic causes [22,23]. Although physical exercise may also cause cTnI release, the consequences and possible prognostic implications regarding future CV events and adverse cardiac remodelling are poorly understood [24,25].

Myocardial injury is defined as an elevated cTnI above the 99th percentile and can be classified as acute or chronic based on the presence of an increase or decrease in cTnI levels. Myocardial injury and evidence of acute myocardial ischaemia (symptoms, ECG abnormalities, imaging abnormalities) define AMI [1,26]. A substantial proportion of patients do not meet the above criteria and require an alternative diagnostic approach. This group consists of patients with unstable angina pectoris or a multitude of other CV or non-CV conditions, requiring distinct therapeutic approaches. Patient sub-stratification is challenged by common symptoms including chest pain and shortness of breath, and by possible pre-existing CAD of unclear relevance in the current setting. The diagnostic follow-up includes echocardiography or computed tomography, which require additional resources and expertise. Particularly in the acute setting, an efficient and accurate initial assessment can improve the subsequent strategy regarding planned follow-up, timely diagnosis, and appropriate treatment. The present study now shows that cTnI below the traditional threshold may help to identify patients at increased risk at an early stage, suggesting that even relatively low levels of cTn may be a risk factor for adverse outcomes in these patients. Although low levels of cTn may help guiding the initiation of specific therapies or taking other preventive measures, it should always be interpreted in the context of other known risk factors for CV disease and mortality and never be used in isolation to guide therapy. While the effect was recapitulated for various lead diagnoses including coronary artery disease, heart failure and valvular heart disease in the present analysis, the individual role in the context of specific diseases should be judged with caution. Of note, the examined cohort represents rather a high-risk population, as evidenced by the significant all-cause mortality

Table 2
Univariate and multivariable regression analysis of detectable troponin below th 99th percentile with incident mortality during follow-up. The hazard ratio was adjusted for age, sex, low-density lipoprotein cholesterol, systolic blood pressure, family history of premature coronary artery disease and smoking status. A second analysis was further stratified by renal function indicated by admission creatinine < vs. ≥ 1.3 mg/dl. CI, confidence interval.

	Hazard ratio (95 % CI)	p-value
Unadjusted	1.78 (1.62–1.96)	p < 0.001
Multivariable adjusted	1.68 (1.53–1.84)	p < 0.001
Multivariable adjusted + creatinine	1.60 (1.45–1.76)	p < 0.001

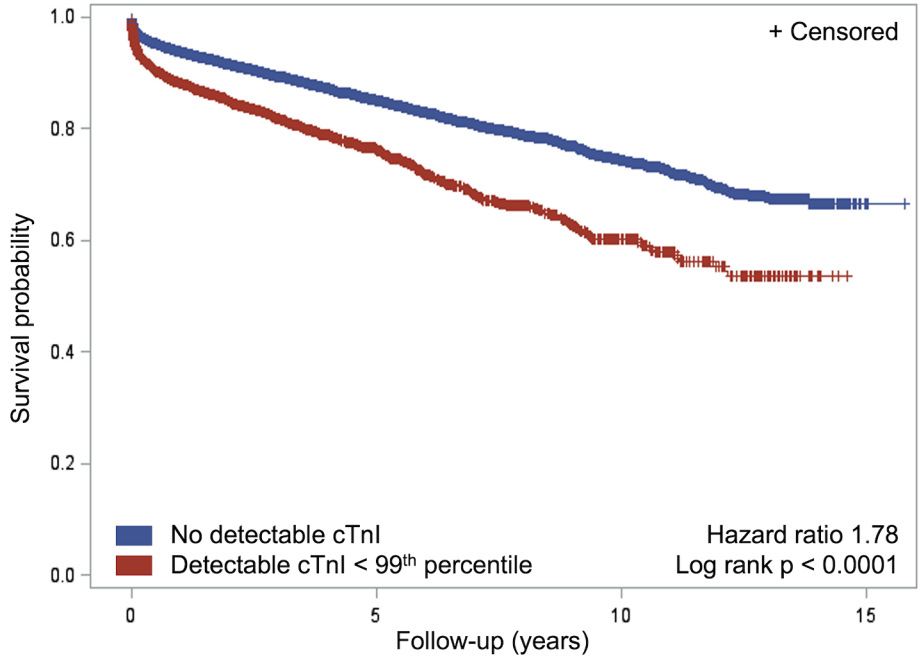

Fig. 2. Kaplan-Meier estimates of survival probability. The panel shows the analysis of survival probability as the primary endpoint in all patients with detectable cTnI below the 99th percentile (n = 2811) in red and all patients without detectable cTnI (11,965). The statistical analysis was performed using the log rank test.

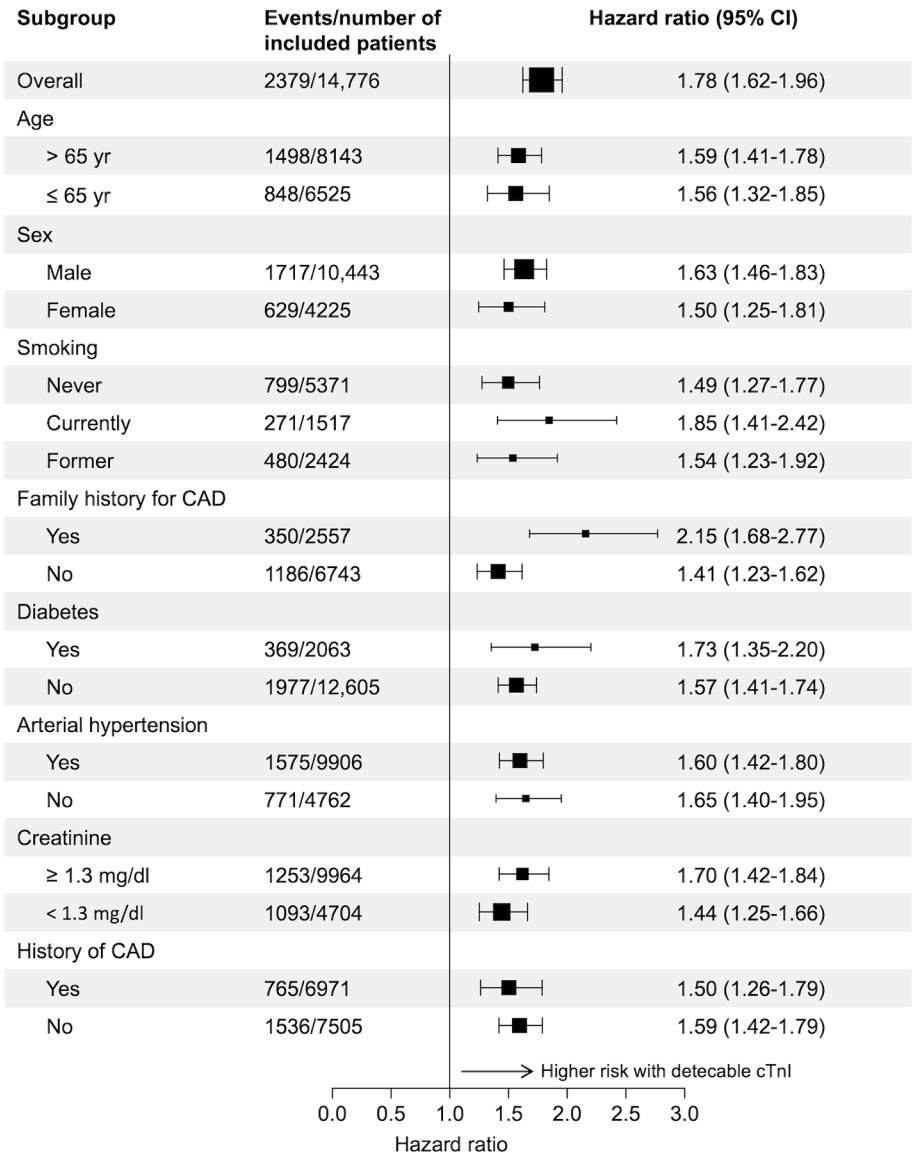

Fig. 3. Hazard ratio for the association of detectable troponin below the 99th percentile with all-cause mortality in relevant subgroups. Individual estimates of different subgroups including relevant cardiovascular risk factors for patients with detectable cTnI below the 99th percentile and patients without detectable cTnI. Events were defined as death from any cause. Data are shown as events and total number of included patients for the respective analysis. The unadjusted analysis including all patients is shown as *Overall*. Results are presented as hazard ratio and 95 % confidence interval (95 % CI). Individual variables are defined as outlined in the Methods section. CAD, coronary artery disease, yr, year old.

Table 3
Subgroup analysis of detectable troponin below the 99th percentile with incident mortality during follow-up stratified for main diagnosis. The table shows the age and sex-adjusted hazard ratio in subgroups of the individual main diagnosis of the respective presentation according to hospital records. CI, confidence interval.

	Hazard ratio (95 % CI)	p-value
Coronary artery disease (n = 7207)	1.613 (1.365–1.906)	p < 0.001
Valvular heart disease (n = 1598)	1.364 (1.077–1.726)	p = 0.010
Heart failure (n = 928)	1.915 (1.443–2.541)	p < 0.001
Arrhythmia (n = 527)	2.248 (1.257–4.018)	p = 0.006
Other (n = 4516)	1.798 (1.543–2.094)	p < 0.001

rate. Thus, it remains to be determined whether the effect applies to a lower-risk populations. The primary use of a non-high-sensitive cTn assay must also be considered for the interpretation of results, but has particular relevance for general emergency departments without a dedicated cardiology department and hospitals without immediate availability of a high-sensitive assay. The increasing use of high-sensitive cTn assays has the potential to further enhance the diagnostic value with improved discrimination, particularly in lower-range cTn elevation, which require validation in future studies.

Several clinical characteristics may influence cTnI levels, as shown in the subgroup analysis. The frequency of detectable cTnI below the 99th percentile compared to no detectable cTnI was altered in the presence of arterial hypertension, hyperlipidaemia, and family history of CAD. It was associated with several laboratory values, including haemoglobin, creatinine, C-reactive protein and BNP [22]. As the complexity of these interactions cannot be appropriately controlled with the used study design, especially in the presence of multiple confounders, our recommendations for clinical practice should be considered with caution. As

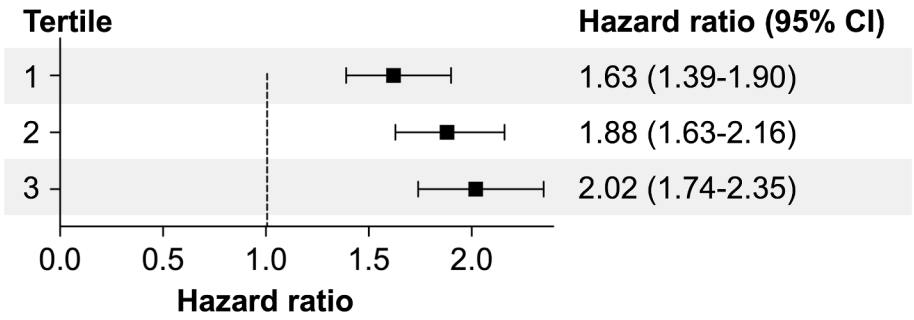

Fig. 4. Tertile analysis for the association of tertiles of detectable troponin below the 99th percentile with incident mortality. Results are presented as hazard ratio and 95 % confidence interval from univariate analysis.

an example, current smokers were shown to have lower cTnI levels than former smokers or patients who had never smoked in previous analysis, while the predictive value of cTnI for CV events was stronger in never/former smokers than in current smokers [27]. In the present study, the proportion of current smokers did not differ between patients with an elevated cTnI below the 99th percentile and those without an elevated cTnI, although this is known to be a relevant risk factor for CV disease and mortality, while the proportion of former smokers was increased in patients with detectable cTnI [27].

For the sole purpose of risk prediction, a detectable cTnI below the 99th percentile may show great potential, especially as a parameter in *state-of-the-art* scoring systems. The complex interplay and the reciprocal correlations between the multitude of risk factors may require novel approaches to provide the most accurate prediction by incorporating all available information [28]. Recent advances in big data and artificial intelligence have made it possible to incorporate a multitude of patient-related factors including lifestyle, clinical characteristics, laboratory values, OMIC data and genetics into complex predictive models. By applying machine learning approaches based on databases like the ECAD registry, these models can achieve a predictive accuracy that is superior to conventional risk scores used in routine clinical practice [29,30]. cTnI along with other relevant patient characteristics to develop predictive models that can improve the accuracy of risk assessment for CV disease. Models can be trained to analyse large datasets of patient records including demographic characteristics, medical history, and further laboratory test results. Models can identify patterns and trends that are associated with an increased risk of death in individual patients, allowing clinicians to make more informed decisions about how best to manage their care.

4.1. Limitations

The retrospective nature of the study may have introduced bias from differences in patient characteristics including main cardiac diagnoses with variable severity or risk factors. The cohort studied can be considered high-risk with high all-cause mortality, and it is uncertain whether the findings can be translated to low-risk cohorts. Selective or incomplete reporting of risk factors and comorbidities may have introduced also reporting bias. The use of two different cTnI assays with different sensitivities and cut-offs may have influenced the identification of eligible patients. Finally, the long observation period may have introduced heterogeneity due to interim changes in guidelines and medical standards, but was necessary to achieve the long follow-up and large number of cases included.

5. Conclusion

A detectable cTnI below the 99th percentile in patients with suspected CV disease indicates an increased risk for all-cause mortality. This risk becomes greater with increasing cTnI levels. More prospective data are required to improve the initial assessment and further diagnostic and therapeutic pathways in this heterogeneous patient population.

CRediT authorship contribution statement

Lars Michel: Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Stefanie Jehn:** Writing – review & editing, Software, Investigation, Formal analysis, Data curation. **Iryna Dykun:** Writing – review & editing, Resources, Methodology. **Markus S. Anker:** Writing – review & editing, Methodology, Conceptualization. **Peter Ferdinandy:** Writing – review & editing, Validation, Methodology. **Dobromir Dobrev:** Writing – review & editing, Supervision, Methodology. **Tienush Rassaf:** Writing – review & editing, Supervision, Software, Resources, Project administration, Conceptualization. **Amir A. Mahabadi:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Matthias Totzeck:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.T. and T.R. report personal fees and others from Edwards, Novartis, Bristol Myers Squibb, Bayer, Daiichi Sankyo und AstraZeneca and Pfizer outside the submitted work. T.R. is a co-founder of Bimyo, a company focusing on the development of cardioprotective peptides. L.M. reports personal fees from Bayer, Alnylam, AstraZeneca, IFFM e. V. and from Bund der Niedergelassenen Kardiologen (BNK) outside the submitted work. M.S.A. reports personal fees from Servier, outside the submitted work. P.F. is the founder and CEO of Pharmahungary Group, a group of R&D companies. All other authors report no conflict of interest. D.D. obtained honoraria for educational lectures from Daiichi Sankyo, all unrelated to this work.

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