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ORIGINAL ARTICLE

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Minor troponin T elevation and mortality in patients with atrial fibrillation presenting to the emergency department

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Abstract

Background: There are limited data on the association of minor troponin elevation in unselected patients with atrial fibrillation (AF) presenting to the emergency department (ED) with adverse events. In this study, we sought to assess the early and mid-term mortality of these patients.

Methods: In this observational study, 2911 patients with AF were admitted to the ED. They were divided into 3 groups based on peak high-sensitivity troponin (TnT) levels: normal (<15 ng/L), 15-50 ng/L and 51-100 ng/L. The primary outcomes of this study were all-cause mortality at 30 days and 1 year.

Results: All-cause mortality was 6.7% (n = 196) at 30 days and 22.2% (n = 646) at 1 year. Mortality rate increased along with increasing levels of TnT irrespective of baseline covariates, primary discharge diagnosis and type of AF. A significant association between TnT levels and all-cause mortality was observed. The adjusted hazard ratio (HR) at 30 days was 6.02 (95% CI 2.62-13.83) for TnT 15-50 ng/L and 11.28 (95% CI 4.87-26.12) for TnT 51-100 ng/L (P<.001 for both) compared to TnT <15 ng/L. At 1 year, the adjusted HRs were 3.08 (95% CI 2.15-4.40) and 5.07 (95% CI 3.49-7.35), respectively (P < .001). When patients with TnT <15 ng/L were divided into two groups at the median value, TnT elevation of 10 to 14 ng/L was also associated with increased 1-year mortality (HR 2.51; 95% CI 1.09-5.74; P = .03).

Conclusions: Among patients with AF admitted to the ED, increased TnT levels were associated with increased early and mid-term all-cause mortality irrespective of baseline covariates and type of AF.

KEYWORDS
atrial fibrillation, mortality, myocardial infarction, troponin

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Clinical trial registration: This study is a pre-specified analysis from the Troponins in Atrial Fibrillation study (Tropo-AF Study, Clinicaltrials.gov Identifier: NCT03683836).

1 | INTRODUCTION

Cardiac troponins are often measured in patients presenting to the emergency department (ED) with symptomatic atrial fibrillation (AF) as a part of routine diagnostic workup.[1,2] Increased troponin level is a common finding in these patients, but only rarely they are suggestive of acute coronary syndrome.[3-6] Irrespective of the cause of troponin elevation, this has been shown to be an independent risk factor for all-cause mortality in several clinical conditions.[7] Still, there are scarce data on the clinical significance of minor troponin elevation in AF patients admitted to the ED. In this study, we sought to investigate the all-cause mortality and hospitalizations for myocardial infarction at 30 days and at 1 year in AF patients presenting in ED with various degrees of minor (≤100 ng/L) high-sensitivity cardiac troponin T (TnT) elevation.

2 | METHODS

This study is a pre-specified analysis from the Troponins in Atrial Fibrillation study (Tropo-AF Study, Clinicaltrials.gov Identifier: NCT03683836). We conducted laboratory

TABLE 1 Baseline characteristics of the study groups

	All patients (n = 2911)	TnT <15 ng/L (n = 795)	TnT 15-50 ng/L (n = 1446)	TnT 51-100 ng/L (n = 670)	*P*-value
Age, years	77.1 ± 10.5	71.0 ± 10.3	78.8 ± 9.6	80.7 ± 9.6	<.001
Females	1457 (50.1)	432 (54.3)	728 (50.3)	298 (44.5)	.001
Permanent AF	1373 (47.0)	262 (33.0)	753 (52.1)	354 (52.8)	<.001
Paroxysmal AF	1211 (41.6)	493 (62.0)	479 (33.1)	239 (35.7)	<.001
New onset AF	327 (11.2)	39 (4.9)	211 (14.6)	77 (11.5)	<.001
AF on admission ECG	2077 (73.8)	474 (62.0)	1116 (79.9)	487 (74.6)	<.001
CHA_2DS_2-VASc	3.89 ± 1.76	3.3 ± 1.85	4.03 ± 1.68	4.29 ± 1.65	<.001
Comorbidities					
Congestive heart failure	610 (21.0)	86 (10.8)	315 (21.8)	209 (31.2)	<.001
Hypertension	1990 (68.4)	505 (63.5)	980 (67.8)	505 (75.4)	<.001
Diabetes mellitus	745 (25.6)	155 (19.5)	377 (26.1)	213 (31.8)	<.001
Coronary artery disease	869 (29.9)	186 (23.4)	444 (30.7)	239 (35.7)	<.001
Prior myocardial infarction	449 (15.4)	99 (12.5)	223 (15.4)	127 (19.0)	.003
Prior stroke/TIA	553 (19.0)	153 (19.2)	281 (19.4)	119 (17.8)	.65
Peripheral artery disease	160 (5.5)	24 (3.0)	85 (5.9)	51 (7.6)	<.001
Active malignancy	128 (4.4)	29 (3.6)	68 (4.7)	31 (4.6)	.339
Main symptoms					
Dyspnoea	823 (28.3)	132 (16.6)	438 (30.3)	253 (37.8)	<.001
Chest pain	513 (17.6)	215 (7.4)	209 (7.2)	89 (3.1)	<.001
Laboratory parameters					
TnT, ng/L	27.0 [14.0-48.0]	10.0 [8.0-12.0]	29.0 [22.0-38.0]	68.0 [58.0-79.0]	<.001
Haemoglobin, g/L	131 [118-144]	138 [128-148]	130 [117-143]	123 [111-138]	<.001
eGFR, ml/min/1.73 m^2	60.0 [44.3-76.7]	71.0 [58.5-83.5]	58.3 [43.0-75.5]	47.8 [33.5-65.9]	<.001
NT-proBNP, ng/L[a]	2930 [1230-5838]	1030 [457-2358]	3140 [1390-5630]	4949 [2115-9645]	<.001
CRP, mg/L[b]	17.5 [4.0-70.0]	4.0 [2.0-14.5]	22.0 [6.0-79.3]	36.0 [10.0-106.0]	<.001
Systolic blood pressure, mmHg[c]	141 [123-161]	144 [126-165]	142 [124-162]	136 [115-157]	<.001
ST depression on admission ECG	220 (7.6)	20 (2.8)	139 (10.5)	61 (10.3)	<.001

Note: Values are n (%), mean ± standard deviation and median [interquartile range, 25th-75th percentiles].

Abbreviations: AF, atrial fibrillation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); NT-proBNP, N-terminal pro-brain natriuretic peptide; TIA, transient ischaemic attack; TnT, high-sensitivity cardiac troponin T.

[a]Data missing on 1507 patients;

[b]Data missing on 261 patients;

[c]Data missing on 352 patients.

database searches to identify AF patients with measured TnT at the Turku University Hospital, Finland, between 1 March 2013 and 11 April 2016. All included patients who had either history of AF or AF were diagnosed on ED admission. Overall, 145 837 TnT measurements were obtained. From these measurements, we identified patients living in the hospital catchment area who had either a prior diagnosis of AF or the diagnosis was made at the index ED visit. Study inclusion criteria also included electrocardiogram (ECG) at admission and at least two serial TnT measurements within 8-72 hours after admission to the ED.

A total of 2911 AF patients fulfilling the inclusion criteria were identified, and their clinical characteristics are presented in Table 1. The diagnosis of AF, either made before or at the time of the ED visit, was confirmed with 12-lead ECG. All individual electronic patient records were reviewed following a standardized protocol to collect information on patient demographics, comorbidities and other clinical and laboratory data of interest from the index hospitalization and outcomes of interest during the follow-up. ECGs were screened for any ST segment depression ≥1 mm in two adjacent leads. AF was defined paroxysmal when it terminates/has terminated spontaneously or with intervention within 7 days of onset. AF was defined permanent when AF has been accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. AF was defined as first diagnosed if not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms. Data on mortality were retrieved from the national statistical institution, Statistics Finland with the follow-up ending on 9 April 2018. Based on this data, follow-up was considered complete in all patients.

All TnT samples were analysed using a commercial high-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany) at our Institution's certified laboratory. Determined by the manufacturer, the 99th percentile upper reference limit was 14 ng/L for the assay. Three study groups were defined on the basis of peak TnT value: patients with normal (<15 ng/L) TnT level, TnT between 15 and 50 ng/L and those with TnT between 51 and 100 ng/L. The main discharge diagnoses were grouped into six categories, that is AF, infections, stroke/transient ischaemic attack, acute coronary syndrome, heart failure and other conditions.[6] The main diagnosis was placed at discretion of the ED physician, and all patients had either a history of AF or were found to have new AF on admission.

The primary outcomes of this analysis were 30-day and 1-year all-cause mortality. Secondary outcomes were all-cause mortality at 3 years as well as myocardial infarction at 30-day and at 1-year follow-up.

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. Informed consent was waived because of the observational and retrospective nature of the study. Reporting of the study conforms to broad EQUATOR guidelines.[8]

2.1 | Statistical analysis

Statistical analysis was performed using SPSS v. 25.0 statistical software (IBM Corporation). Continuous variables are reported as the mean and standard deviation (SD) if normally distributed or as the median and interquartile range (IQR) if skewed. Dichotomous variables are reported as absolute numbers and percentages. For all variables with more than 0.5% missing data, the exact number of patients with missing data is reported. The chi-square test and Fisher's exact test were used for analysing categorical variables as appropriate. Continuous variables were evaluated using the Kruskal-Wallis test. The Kaplan-Meier method was used to estimate 30-day and 1-year all-cause mortality rates, and the log-rank test was used for comparison across the groups. The adjustments for Cox proportional hazards model were made for significant ($P < .1$) univariate predictors of mortality: age >75 years, sex, AF at admission, heart failure, hypertension, diabetes mellitus, coronary artery disease, prior myocardial infarction, prior stroke or transient ischaemic attack, peripheral artery disease, active malignancy, dyspnoea, chest pain, heart rate >120/min at admission, ST depression on admission ECG, anaemia, CRP >30 mg/L and eGFR <30 mL/min/1.73 m^2. The final regression model was selected using the stepwise method with backward Wald elimination. Risk estimates are reported as hazard ratio (HR) with 95% confidence interval (CI). $P < .05$ was set for statistical significance.

3 | RESULTS

3.1 | Baseline data

Overall, 2911 patients with AF were included in the present study. TnT was undetectably low (<5 ng/L) in 59 (2%) patients, within normal range (<15 ng/L) in 795 (27.3%) patients, 15-50 ng/L in 1446 (49.7%) patients and 51-100 ng/L in 670 (23.0%) patients (Table 1).

3.2 | 30-day outcome

At 30 days, the overall mortality rate was 6.7% (n = 196). Thirty-day mortality was 0.9% (n = 7) in patients with TnT <15 ng/L, 6.8% (n = 98) in patients with TnT 15-50 ng/L and 13.6% (n = 91) in patients with TnT 51-100 ng/L.

The 30-day admission rate for myocardial infarction was low (0.2%), and it was not associated with peak TnT levels ($P = .14$).

3.3 | Mid-term outcome

The median duration of follow-up was 2.9 (IQR 2.2-3.7) years. The overall mortality was 22.2% (n = 644) at 1 year and 39.9% (n = 1057) at 3 years.

At 1 year, mortality was 5.4% (n = 43) in patients with TnT <15 ng/L, 23.4% (n = 336) in patients with TnT 15-50 ng/L and 39.6% (n = 265) in patients with TnT 51-100 ng/L ($P < .001$) (Suppl. Figure 1).

At 1 year, the rate of myocardial infarction in the three study groups with increasing TnT values was 0.6%,1.7% to 2.8%, respectively ($P = .004$).

3.4 | Results of multivariable analysis

Minor TnT elevation was associated with mortality at 30 days and 1 year when adjusted for multiple covariates (Table 2). The adjusted HRs for 30-day mortality were 6.02 (95% CI 2.62-13.8) for TnT 15-50 ng/L and 11.3 (95% CI 4.87-26.1) for TnT 51-100 ng/L ($P < .001$ for both) compared with patients with TnT <15 ng/L. The adjusted HRs for 1-year mortality were 3.08 (95% CI 2.15-4.40) for TnT 15-50 ng/L and 5.07 (95% CI 3.49-7.35) for TnT 51-100 ng/L compared with patients with TnT <15 ng/L (Figure 1; Table 2). This effect persisted at 3 years (Table 2). Besides minor TnT elevation, active malignancy, ST depression on admission ECG and CRP >30 mg/L on admission were independently tied to 30-day mortality. The most important other independent associations with 1-year mortality were active malignancy, age >75 years and congestive heart failure (Table 2). The association of TnT elevation with mortality was similar regardless of the type of AF (Figure 1) or discharge diagnosis (Figure 2).

When patients with TnT <15 ng/L were dichotomized according to the median value of peak TnT, patients with a TnT level ranging from 10 to 14 ng/L had a significantly increased risk of 1-year mortality (HR 2.51; 95% CI 1.09-5.74; $P = .03$), but not of 30-day mortality (HR 1.41; 95% CI 0.26-7.72; $P = .69$) compared to patients with lower TnT levels.

4 | DISCUSSION

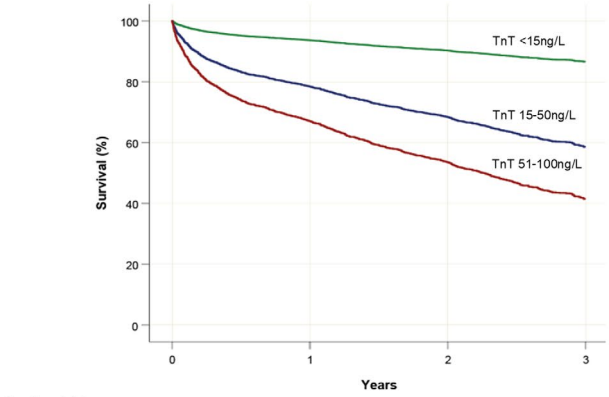
The main finding of our study was that minor TnT elevation was associated with both short- and mid-term mortality in AF patients irrespective of their discharge diagnoses and type of AF. The risk estimates increased along with the TnT levels and extended also to the subset of patients with TnT below 15 ng/L. Acute coronary syndrome was an infrequent cause of minor TnT elevation (Figure 2), and the incidence of myocardial infarction during 30-day follow-up was low and not related to minor TnT elevation during the index ED visit.

TABLE 2 Independent risk factors for all-cause mortality at different study intervals in AF patients presenting to the emergency department

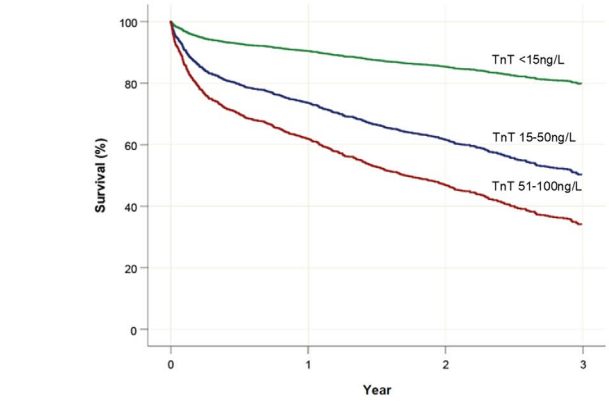
Outcomes	*P*-value	Adjusted HR (95% CI)
30-d mortality		
TnT levels		
TnT 15-50 ng/L	<.001	6.02 (2.62-13.83)
TnT 51-100 ng/L	<.001	11.28 (4.87-26.12)
Active malignancy	<.001	2.86 (1.82-4.49)
ST segment depression	.003	1.83 (1.23-2.74)
CRP >30 mg/L	.008	1.52 (1.11-2.07)
Heart failure	.06	1.37 (0.99-1.89)
1-y mortality		
TnT levels		
TnT 15-50 ng/L	<.001	3.08 (2.15-4.40)
TnT 51-100 ng/L	<.001	5.07 (3.49-7.35)
Active malignancy	<.001	2.56 (1.93-3.39)
Age >75 y	<.001	1.79 (1.44-2.22)
Heart failure	<.001	1.45 (1.21-1.74)
Anaemia[a]	.001	1.34 (1.13-1.59)
ST depression on admission ECG	.039	1.31 (1.01-1.69)
CRP >30 mg/L	.006	1.29 (1.01-1.54)
AF on admission	.04	1.26 (1.01-1.56)
Chest pain	.009	0.69 (0.53-0.91)
3-y mortality		
TnT levels		
TnT 15-50 ng/L	<.001	3.21 (2.51-4.11)
TnT 51-100 ng/L	<.001	5.33 (4.11-6.92)
Active malignancy	.001	2.31 (1.80-2.97)
Age >75 y	<.001	1.68 (1.43-1.98)
Heart failure	<.001	1.53 (1.32-1.77)
Prior stroke or transient ischaemic attack	<.001	1.36 (1.12-1.58)
Anaemia[a]	<.001	1.35(1.18-1.54)
Prior myocardial infarction	.004	1.28 (1.08-1.52)

Note.: Abbreviations: HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; CRP, C-reactive protein; and TnT, high-sensitivity cardiac troponin T.

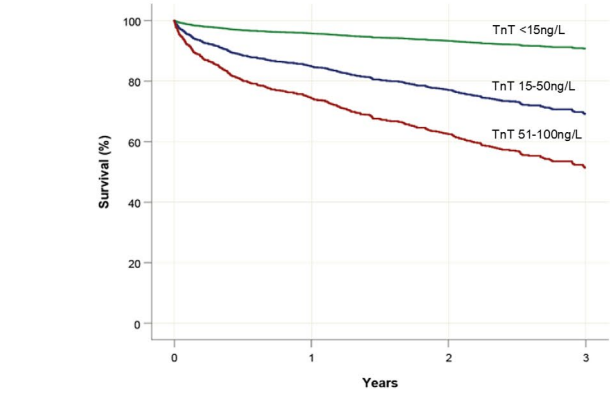
[a]Haemoglobin level below 120g/L in females and 130 g/L in males. The adjustments for Cox proportional hazards model were made for significant ($P < .1$) univariate predictors of mortality: age >75 y, sex, AF at admission, heart failure, hypertension, diabetes mellitus, coronary artery disease, prior myocardial infarction, prior stroke or transient ischaemic attack, peripheral artery disease, active malignancy, dyspnoea, chest pain, heart rate >120/min at admission, ST depression on admission ECG, anaemia, CRP >30 mg/L and eGFR <30 mL/min/1.73 m^2. The final regression model was selected using the stepwise method with backward Wald elimination. Risk estimates are reported as HR with 95% confidence interval.



Number at risk				
TnT<15 ng/L	795	752	725	481
TnT 15-50 ng/L	1446	1105	733	303
TnT 51-100 ng/L	670	404	272	113



Number at risk				
TnT<15 ng/L	263	239	228	145
TnT 15-50 ng/L	756	550	348	128
TnT 51-100 ng/L	354	202	134	56



Number at risk				
TnT<15 ng/L	493	474	459	308
TnT 15-50 ng/L	479	389	267	133
TnT 51-100 ng/L	239	153	101	42

FIGURE 1 Cox adjusted survival curves for all AF patients (upper panel), patients with permanent AF (middle panel) and patients with paroxysmal AF (lower panel). TnT, high-sensitivity cardiac troponin T

In addition to their primary diagnostic use, cardiac troponins provide important prognostic information in patients with acute coronary syndromes.[9,10] Later, troponin elevations have been linked to long-term adverse outcomes in stable coronary artery disease and chronic heart failure and even in general populations.[11-14] Among patients with AF, high-sensitivity measurement of TnT has been shown to improve the long-term risk stratification for stroke, bleeding and cardiovascular mortality beyond clinical risk scores.[3]

At present, cardiac troponin testing is frequently used in the ED in the absence of symptoms suggestive of acute coronary syndromes. The clinical significance of mildly elevated troponin values in patients with AF is unclear, and minor troponin

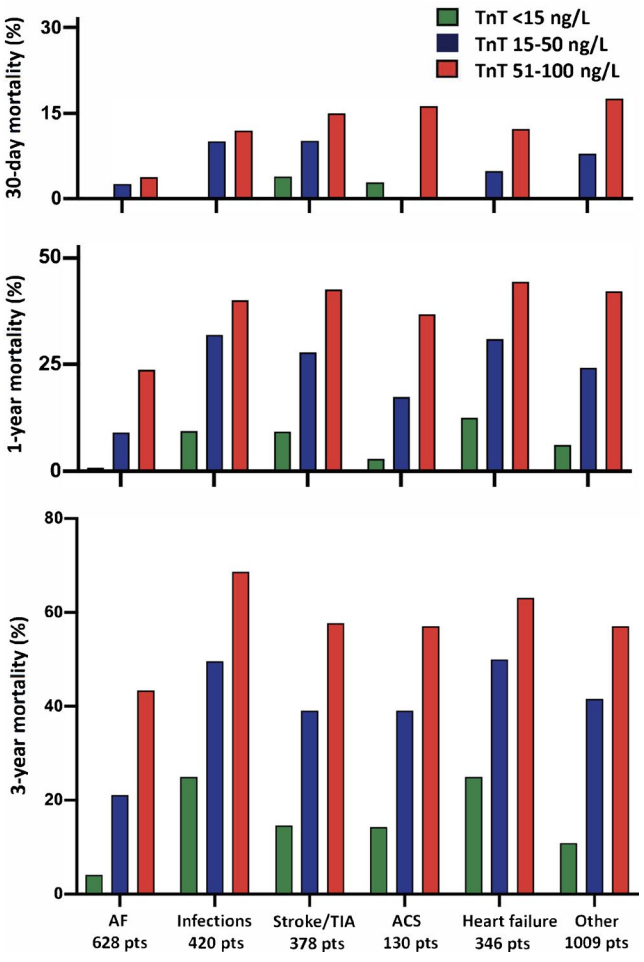


FIGURE 2 Thirty-day (upper panel), 1-y (middle panel) and 3-y (lower panel) mortality according to primary discharge diagnosis at ED. AF, atrial fibrillation; TIA, transient ischaemic attack; ACS, acute coronary syndrome; ED, emergency department; and TnT, high-sensitivity cardiac troponin T. All patients had AF, and in the AF group, AF was the primary cause of ED visit

elevations are common also in a wide variety of other noncardiac conditions, such as systemic infection, renal failure, cerebrovascular accident and even after extreme physical exercise.[15-18] In an early study of van den Bos et al,[19] minor troponin I elevations assessed by a less sensitive assay predicted mortality and cardiac events in AF patients in the acute setting. In other studies in the ED setting, minimal troponin elevations were associated only with a nonsignificant trend towards higher incidence of adverse cardiac events and mortality[20,21] and were not associated with cardiovascular events or mortality in patients with AF lasting less than 48 hours.[22] Stoyanov et al[23] showed in a retrospective study that even minor elevations of TnT levels are associated with higher mortality in patients with AF, and provide added prognostic information independent of major cardiovascular risk factors and clinical characteristics.

The present findings provide insights on the early and mid-term outcome of AF patients presenting to the ED with TnT elevation. We have stratified the outcome of these patients with increasing levels of TnT across a number of clinical conditions causing the ED visit in a large and unselected patient population with comprehensive baseline data and complete long-term follow-up information. Acute coronary syndrome as the cause of their index ED visit was diagnosed only in a minority of our patients and, consistent with this finding, coronary ischaemic events were infrequent in the mid-term follow-up. We provided evidence that even minor TnT elevation was associated with increased mortality also in patients with noncardiac causes for ED visit (Figure 2) and regardless of the type of AF (Figure 1). The association between TnT and increased mortality extended also to patients with minimally increased TnT levels still within laboratory normal range (10-14 ng/L) in whom the 1-year mortality was 2.5-fold higher than in patients with lower-normal TnT values. As expected, survival was highest in patients with AF as their main discharge diagnosis. In the other diagnostic categories, TnT level 51-100 ng/L was linked to poor outcome with a 1-year mortality exceeding 35% (Figure 2).

The mechanisms by which cardiac troponin is released from myocytes in AF patients with acute or chronic comorbidities are not known, but there is evidence of other mechanisms besides myocardial necrosis. The proposed mechanisms include for example reduced myocardial perfusion during AF and co-existence of coronary artery disease. However, it is likely that the mechanisms are multifactorial with different contributing factors.[24-26] It seems, however, that the prognostic significance is similar regardless of the cause of troponin release.

4.1 | Study limitations

This is a retrospective study including AF patients with a variety of acute conditions and having at least two TnT measurements during the hospital visit. Patients were treated by ED physicians with no strict institutional protocol for TnT testing. The main strength of this study is the comprehensive data collected from patient records and complete follow-up data, which was available in all patients.

5 | CONCLUSIONS

Minor troponin elevations detected at the ED visit were associated with increased 30-day and 1-year mortality in AF patients irrespective of the discharge diagnoses and type of AF. Acute coronary syndrome was an infrequent cause of minor TnT elevation, and the incidence of myocardial infarction during 30-day follow-up was low and not related to minor TnT elevation.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT

Reporting of the study conforms to broad EQUATOR guidelines. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. Informed consent was waived because of the observational and retrospective nature of the study.

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CONFLICT OF INTEREST

Tuomas Paana: none; Samuli Jaakkola: lecture fees from MSD, Bayer, BMS-Pfizer and AstraZeneca; Ilpo Nuotio: none; Tuomas O. Kiviniemi: received research grants from the Finnish Medical Foundation, the Finnish Foundation for Cardiovascular Research, Finnish Cardiac Society, the Emil Aaltonen Foundation, the Maud Kuistila Foundation and unrestricted grants for investigator-initiated trials from AtriCure Ltd and Vifor Pharma; received lecture fees from Bayer, Boehringer Ingelheim, MSD, Astra Zeneca, St Jude Medical and Bristol-Myers-Squibb-Pfizer; and a member of the advisory board of Boehringer Ingelheim, and MSD; Tuijan Vasankari: none; Fausto Biancari: none; and KE Juhani Airaksinen: research grants from the Finnish Foundation for Cardiovascular Research, lecture fees from Bayer, Pfizer and Boehringer Ingelheim, a member in the advisory boards for Bayer, Pfizer and Astra Zeneca.

DATA AVAILABILITY STATEMENT

Access to data is regulated by Finnish law. Data are available from the Turku University Hospital for researchers who meet the criteria as required by the Finnish law to access

confidential data. Contact person who will distribute data upon request to qualified researchers: Tuija Vasankari, Heart Center, Turku University Hospital, PO BOX 52, FIN-20521, Turku, Finland; tuija.vasankari@tyks.fi.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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