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The impact of diabetes mellitus on the outcome of troponin-positive patients with non-obstructive coronary arteries

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ABSTRACT

Background: Diabetes mellitus is a major cardiovascular risk factor for the development of coronary artery disease, but knowledge about the impact of diabetes mellitus on the outcome of patients with myocardial infarction with non-obstructive coronary arteries is limited. The aim of this study was to investigate the prognostic impact of diabetes mellitus on in- and out-of-hospital adverse events in troponin-positive patients with non-obstructive coronary arteries.

Methods and Results: A total of 373 troponin-positive patients with non-obstructive coronary arteries between 2010 and 2021 at Bergmannsheil University Hospital Bochum were enrolled, including 65 diabetics and 307 nondiabetics. The median follow-up was 6.2 years. The primary study end point was a composite of in-hospital major adverse cardiovascular events (MACE). Secondary endpoints covered MACE during follow-up.

Mean age of the study cohort was 62.9 years and 49.3 % were male. Although the overall rate of in-hospital MACE was higher in diabetics (41.5 %) than in non-diabetics (33.9 %), this difference did not reach statistical significance ($p = 0.240$). The in-hospital mortality rate was low in both groups, 0 % of diabetes group versus 2.9 % of non-diabetic patients. During follow-up, diabetic patients had a significantly higher rate of MACE (51.9 % vs. 31.1 %, $p = 0.004$) and a significantly higher all-cause mortality rate than non-diabetic patients (42.3 % vs. 20.1 %, $p < 0.001$).

Conclusion: Our study reveals that the impact of diabetes mellitus on cardiovascular outcomes in troponin-positive patients with non-obstructive coronary arteries intensifies over the long term, leading to increased rates of both cardiovascular adverse events and overall mortality.

1. Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) addresses a clinical scenario characterized by a patient presenting with symptoms suggestive of acute coronary syndrome, elevated troponin levels, and non-obstructive coronary arteries on coronary angiography (defined as coronary artery stenosis < 50 % in one of the major epicardial vessels) [1,2]. The reported prevalence of MINOCA varies widely in different studies, ranging from approximately 1 % to 14 % of patients with acute coronary syndrome undergoing coronary angiography [1].

MINOCA is a composite term that encompasses a wide range of underlying conditions, and thus a very heterogeneous patient population [1]. It includes both coronary and non-coronary pathologies, involving

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both cardiac and extracardiac disorders [1]. After unobtrusive coronary angiography, MINOCA serves as a working diagnosis rather than a definitive diagnosis. Clinicians need to perform additional evaluations and investigations to uncover the cause of MINOCA, including the completion of further imaging studies like MRI, to establish a more definitive diagnosis and, consequently, appropriate patient treatment [1,2].

Studies demonstrate that compared with patients with myocardial infarction and obstructive coronary artery disease (CAD), MINOCA patients are mostly younger, more often female, not obese, non-smokers, without arterial hypertension or chronic kidney disease, in summary, without traditional cardiovascular risk factors [3–9]. They also have a significantly higher prevalence of non-ST-segment-elevation myocardial infarction than ST-segment-elevation myocardial infarction [8,10]. Prognosis appears to be more favourable for MINOCA patients, with a one-year mortality of 3.5 %, than for myocardial infarction patients with CAD (one-year mortality: 6.7 %) [6,11,12]. However, the survival rate of MINOCA patients remains worse compared with healthy individuals [6].

Interestingly, MINOCA seems to be more frequent in non-diabetics [3,5,6,8,13], whereas diabetes is a leading risk factor for the development of myocardial infarction with obstructive CAD [3,10,13]. While diabetes is well-established as a contributing risk factor for CAD, other cardiovascular diseases, and overall increased mortality, the impact of diabetes in patients with MINOCA is unknown.

The present study aimed to evaluate the prognostic impact of diabetes mellitus, a major cardiovascular risk factor, on intra- and extrahospital complications and long-term outcome, including mortality, in troponin-positive patients with non-obstructive CAD.

2. Methods

In this study, we retrospectively examined patients that were troponin-positive at admission and presented with non-obstructive coronary arteries in angiography at Bergmannsheil University Hospital Bochum from January 2010 to April 2021. The patients provided informed consent. Each patient's medical background, medications, laboratory results, ECG, and echocardiography were documented during their hospital stay. This investigation involved a retrospective analysis of clinical data conducted at a single center. Approval for the study was granted by the local ethics committee of the Ruhr University Bochum.

2.1. Inclusion and exclusion criteria, follow-up, and study endpoints

This study included troponin-positive patients meeting the criteria for non-obstructive CAD after coronary angiography. MINOCA served as a working diagnosis in these patients: Firstly, cardiac troponin levels needed to be elevated or decreasing, with at least one value surpassing the 99th percentile. Secondly, clinical signs of myocardial infarction had to be evident, indicated by at least one of the following conditions: symptoms of myocardial ischemia, new ischemic changes on the electrocardiogram, pathological Q waves, evidence of new loss of viable myocardium or new regional wall motion abnormalities suggestive of an ischemic cause, or evidence of coronary thrombus by angiography or autopsy. Additionally, patients undergoing coronary angiography were required to have no coronary artery obstruction (stenosis < 50 %) [1,2].

The diagnosis of troponin-positive with non-obstructive CAD was independently established by an experienced cardiologist and a graduate student, based on the assessment of coronary angiograms, echocardiograms, ECGs, and laboratory reports. The finalized patient cohort was then segregated into diabetic and non-diabetic groups for analysis.

Exclusions comprised patients for whom alternative diagnoses were conceivable, causing the clinical presentation of troponin-positivity. Those with obstructive CAD, below 18 years, and those with incomplete datasets were also excluded, along with individuals having severe concomitant diseases significantly limiting life expectancy (<2 years), such as advanced tumour disease.

The primary endpoint was the incidence of major adverse cardiovascular events (MACE) during hospitalization, encompassing stroke, cardiopulmonary resuscitation, cardiogenic shock, pulmonary oedema, invasive and non-invasive ventilation, left ventricular thrombus, thromboembolic events, life-threatening arrhythmias, supraventricular arrhythmias, and all-cause mortality. The secondary endpoint covered MACE during follow-up, including stroke, thromboembolic events, recurrence of troponin-positive with non-obstructive CAD, percutaneous coronary intervention, cardiac arrest, and all-cause mortality. Follow-up occurred between May and September 2023, utilizing data from post-presentation/hospitalization in the university clinic and/or telephone contact with patients. In cases of deceased patients, contact was established with the patients' primary care physicians.

2.2. Statistics

Statistical analysis was performed using SPSS Statistics 23.0 software. Continuous variables with normal distribution were presented as mean ± standard deviation, whereas continuous variables with non-normal distribution were presented as median (interquartile range). Categorical variables were reported as number as well as relative frequency (%). The Kolmogorov-Smirnov test was used to assess normality. Continuous variables with normal and nonnormal distributions were compared using Student's t test for independent samples or Mann-Whitney U test. Categorical variables were compared with either the chi-square test or Fisher's exact test. Kaplan-Meier analyses were used to assess the prognostic impact of diabetes mellitus on the outcome. A two-sided p value < 0.05 was considered significant. All probability values reported are 2-sided.

3. Results

3.1. Baseline characteristics of the cohort

24,775 patients who underwent coronary angiography from 2010 to 2021 were screened for this study. The final study population consisted of 373 patients with a mean follow-up period of 6.2 ± 3.1 years who were troponin-positive at initial presentation and had non-obstructive CAD, including 65 diabetics and 307 nondiabetics (Fig. 1). The mean age for diabetic patients was 68 ± 13 years, while non-diabetic patients had a mean age of 62 ± 16 years. Gender distribution exhibited no significant difference between diabetic and non-diabetic groups (male: 52.3 %).

The prevalence of angina pectoris, dyspnoea, and palpitations did not significantly differ between diabetic and non-diabetic groups.

Diabetic patients had a higher mean heart rate (97 ± 33 beats per minute) compared to non-diabetic patients (88 ± 28 beats per minute) ($p = 0.020$). Systolic and diastolic blood pressure did not show significant differences between the two groups.

ECG data (presence of ST-segment elevation and inverted T-waves) were similar between diabetic and non-diabetic patients.

Diabetic patients presented with a trend towards lower smoking prevalence (13.9 %) compared to non-diabetic patients (25.1 %) ($p = 0.051$). Obesity (BMI > 30 kg/m^2), hypertension, neurological disease, kidney disease, and atrial fibrillation were significantly more prevalent in diabetic patients.

Diabetic patients had significantly lower levels of creatine phosphokinase (CK), whereas troponin and BNP levels were similar between the groups. Furthermore, diabetics had significantly higher thyroid-stimulating hormone (TSH) levels than non-diabetics.

Echocardiography data including left ventricular ejection fraction, left ventricular hypertrophy, and cardiac valve regurgitations did not significantly differ between diabetic and non-diabetic patients. The mean left ventricular ejection fraction was 35.3 % in diabetic patients and 37.3 % in non-diabetic patients (Table 1).

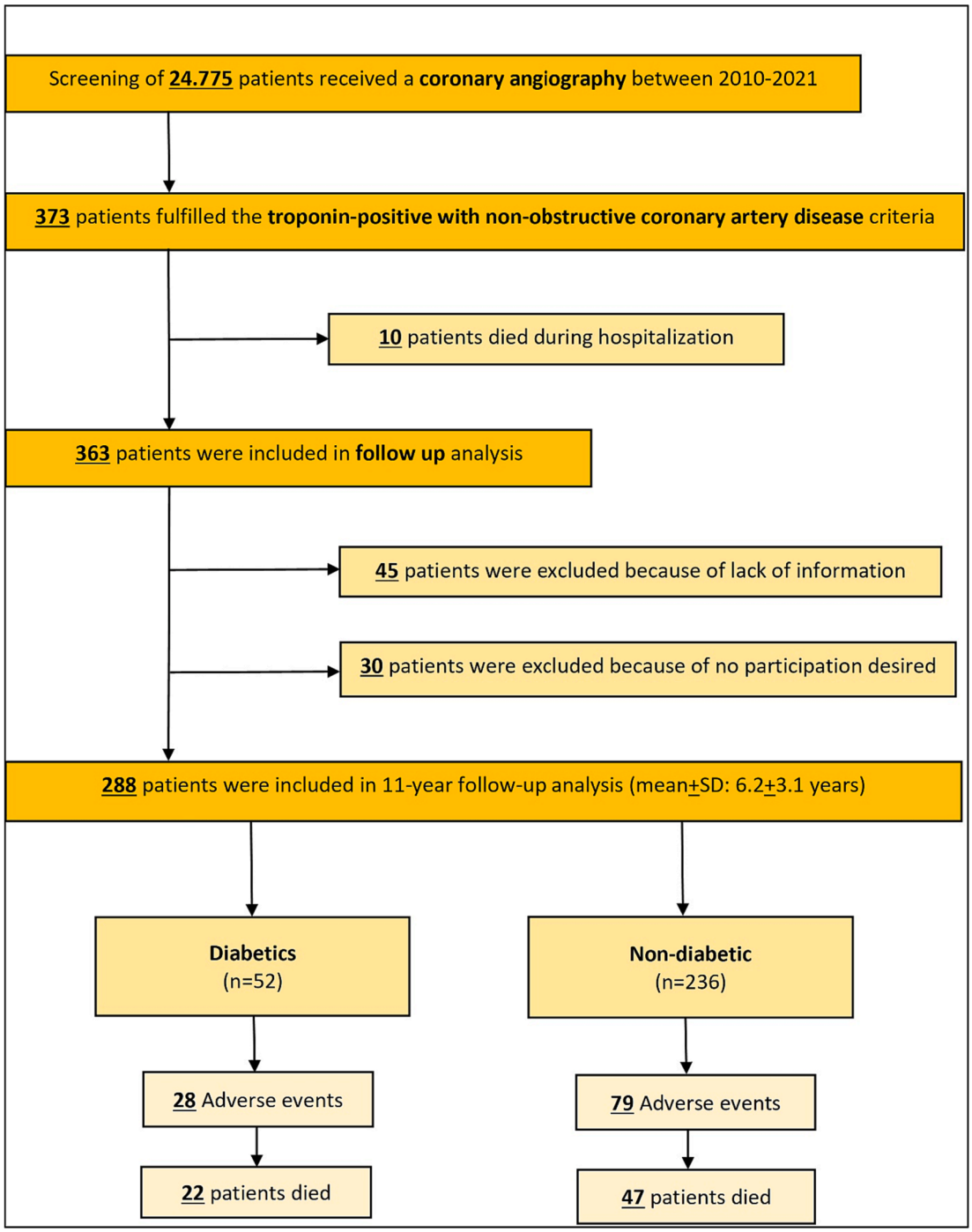

Fig. 1. Flow chart presenting the screened data and included patients.

3.2. Medication on admission and at discharge

The analysis of medication patterns at admission revealed notable differences between diabetic and non-diabetic patients. Diabetics were significantly more frequently prescribed beta-blockers (47.7 % vs. 32.4 %), angiotensin converting enzyme inhibitors (54.7 % vs. 28.1 %), calcium channel blockers (36.9 % vs. 16.3 %), and diuretics (47.7 % vs. 22.6 %) compared to non-diabetics. Anticoagulants were also more commonly prescribed to diabetics (26.2 % vs. 13.4 %). Aspirin demonstrated a significant difference with higher prescription rates in diabetic patients (32.3 % vs. 18.6 %). However, there were no significant differences in the prescription of angiotensin receptor blockers, alpha-2 Agonist, and antiarrhythmics between the two groups (Table 1).

At discharge, the prescription patterns of diabetics and nondiabetics converged more closely. While beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were prescribed more frequently overall, but no significant differences were observed, calcium channel blockers (52.3 % vs. 21.5 %) and diuretics (70.8 % vs. 39.1 %) continued to be prescribed significantly more often to diabetics. Anticoagulants (36.9 % vs. 26.1 %) and aspirin (56.9 % vs. 45.0 %) continued to be prescribed more frequently to diabetics, but without statistical significance anymore. Of note, antiarrhythmics were prescribed significantly more often in diabetic patients at discharge (15.4 % vs. 5.2 %). The prescription rates of clopidogrel and prasugrel were similar between the groups (Supplemental Table 1).

Table 1
Baseline characteristics of 373 troponin-positive patients with non-obstructive coronary artery disease.

Variables	Diabetic (n = 65)	Non-diabetic (n = 307)	p value
Demographics			
Age, mean ± SD	68 ± 13	62 ± 16	0.092
Male, n (%)	34 (52.3)	150 (48.9)	0.614
Symptoms, n (%)			
Angina pectoris	37 (58.7)	189 (62.4)	0.588
Dyspnoa	32 (50.0)	132 (43.4)	0.336
Palpations	9 (14.3)	36 (11.8)	0.597
Clinic parameter			
Systolic BP, mmHg	149 ± 28	146 ± 70	0.762
Diastolic BP, mmHg	85 ± 17	85 ± 18	0.982
Heart rate, bpm	97 ± 33	88 ± 28	**0.020**
ECG Data, n (%)			
ST-segment elevation	6 (9.2)	49 (16)	0.165
Inversed T-Waves	35 (53.9)	147 (48)	0.395
Medical history, n (%)			
Smoking	9 (13.9)	76 (25.1)	0.051
Obesity (BMI > 30 kg/m^2)	37 (56.9)	74 (24.1)	**<0.001**
Hypertension	58 (89.2)	195 (63.7)	**<0.001**
COPD	5 (7.7)	42 (13.7)	0.187
Bronchial Asthma	8 (12.3)	27 (8.8)	0.283
History of malignancy	8 (12.3)	39 (12.8)	0.916
Neurological disease	23 (35.4)	67 (21.9)	**0.021**
Kidney disease	17 (26.2)	36 (11.7)	**0.003**
Autoimmune disease	4 (6.2)	13 (4.3)	0.505
Supraventricular arrhythmias*	17 (26.2)	40 (13.1)	**0.008**
Atrial fibrillation	17 (26.2)	40 (13.1)	**0.008**
Atrial flutter	0 (0)	0 (0)	0
Laboratory values, median ± IQR			
Troponin (µg/L)	0.1 ± 0.2	0.1 ± 1.3	0.235
Creatine phosphatkinase (µmol/sL)	3.2 ± 2.9	3.8 ± 3	**0.037**
BNP (pmol/L)	24.5 ± 88	16 ± 45.1	0.342
TSH (mIU/L)	1.6 ± 2.1	1.2 ± 1.7	**0.018**
fT3 (pmol/L)	5 ± 1.2	5.4 ± 1.2	0.883
fT4 (pmol/L)	12.8 ± 3.9	14.1 ± 5.1	0.377
Echocardiography data, n (%)			
Left ventricular EF % (LV EF)	35.3 ± 25	37.3 ± 26	0.701
Left ventricular hypertrophy (LVH)	24 (38.1)	78 (26.9)	0.076
Drugs on admission, n (%)			
Beta-blocker	31 (47.7)	99 (32.4)	**0.019**
ACE inhibitor	35 (54.7)	86 (28.1)	**<0.001**
Angiotensin receptor blocker	14 (21.5)	42 (13.7)	0.110
Calcium channel blocker	24 (36.9)	50 (16.3)	**<0.001**
Diuretics	31 (47.7)	69 (22.6)	**<0.001**
a2 Agonist	5 (7.7)	9 (2.9)	0.068
Anticoagulants**	17 (26.2)	41 (13.4)	**0.010**
Aspirin	21 (32.3)	57 (18.6)	**0.014**
Antiarrhythmics***	1 (1.5)	8 (2.6)	1.000

SD, Standard deviation; **BP**, blood pressure; **ECG**, Electrocardiogram; **BNP**, brain natriuretic Peptide; **LV EF**, Ejection fraction; **BMI**, body-mass-index; **COPD**, Chronic obstructive pulmonary disease; **ACE**, Angiotensin-converting-enzyme; *, only one supraventricular arrhythmia is counted per patient (even if one patient has several arrhythmias at the same time); ** cumarine, heparin, selective factor 10-blocker, direct thrombin inhibitors; ***, Ivabradin, Flecainid, Sotalol, Dronedaron, Digitalis.

3.3. In-hospital events and treatment approaches

In-hospital MACE rate as the primary study endpoint was higher in diabetic patients (41.5 %) compared to non-diabetics (33.9 %), though the difference was not statistically significant (p = 0.240). Specific adverse events, including stroke, cardiopulmonary resuscitation, cardiogenic shock, pulmonary oedema, invasive and non-invasive ventilation, left ventricular thrombus, and thromboembolic events, and malignant cardiac arrhythmias, demonstrated no significant differences between diabetic and non-diabetic groups. Supraventricular arrhythmias, including atrial fibrillation and flutter, had slightly higher occurrences in diabetic patients, but the difference was not statistically significant. In-hospital death rates were notably low for both groups, with no diabetic patients experiencing in-hospital death, while 2.9 % of non-diabetic patients did (Supplemental Table 2).

The follow-up left ventricular ejection fraction during hospitalisation were similar between diabetic and non-diabetic patients (47.1 ± 14.0 % vs. 49.3 ± 14.8 %, p = 0.492). Subgroup analysis based on heart failure classification (heart failure with preserved / mildly reduced / reduced ejection fraction) presented no significant differences between diabetic and non-diabetic groups. Cardioversion rates were slightly higher in diabetic patients (23.0 %) compared to non-diabetic patients (16.0 %), but the difference was not statistically significant. The rates of receiving a pacemaker (8.2 % vs. 6.2 %) or a wearable cardioverter defibrillator (3.3 % vs. 3.3 %) were comparable between diabetic and non-diabetic patients (Supplemental Table 3).

3.4. Extra-hospital events during follow-up

Diabetic patients experienced a significantly higher rate of MACE (stroke, thromboembolic events, recurrence of troponin-positive with non-obstructive CAD, percutaneous coronary intervention, cardiac arrest, and all-cause mortality) during follow-up compared to non-diabetic patients (51.9 % vs. 31.1 %). There were no significant differences in the incidence of stroke, thromboembolic events, recurrence of troponin-positive with non-obstructive CAD, and cardiac arrest between diabetic and non-diabetic patients. Percutaneous coronary intervention rates were higher in diabetic patients, but the difference was not statistically significant (11.4 % vs. 6.5 %).

Diabetic patients presented with a significantly higher rate of overall death compared to non-diabetic patients (42.3 % vs. 20.1 %). While there was no significant difference in cardiac-caused deaths between the two groups (2.9 % vs. 2.0 %), non-cardiac caused deaths, however, were more prevalent in diabetic patients, although the difference did not reach statistical significance (11.4 % vs. 4.0 %, p = 0.086) (Supplemental Table 4, Fig. 2).

4. Discussion

The present study examined the prognostic impact of diabetes mellitus, an important cardiovascular risk factor, on intra- and extra-hospital complications and long-term outcome, including mortality, in 373 troponin-positive patients with non-obstructive CAD. The main findings of our study were:

1) While the overall in-hospital MACE rate was higher in diabetic patients than non-diabetics, the difference was not statistically significant. Specific adverse events showed no significant differences between the two groups, except for a slightly higher occurrence of supraventricular arrhythmias in diabetic patients. In-hospital death rates were low, with no deaths among diabetic patients and a 2.9 % rate in non-diabetic patients.

2) Diabetic patients had a significantly higher MACE rate compared to non-diabetic patients during follow-up. While there were no significant differences in specific events like stroke or cardiac arrest, diabetic patients showed a higher overall death rate. Non-cardiac caused deaths were more prevalent in diabetic patients, though not statistically significant.

Previous research has demonstrated that the clinical characteristics of MINOCA patients differ from the conventional profile of individuals at risk for myocardial infarction with CAD. MINOCA patients are more likely to be younger, female, not obese, non-smokers, non-diabetic and present less frequently with kidney disease and cerebrovascular diseases [3–10]. Hence, the lower prevalence of traditional cardiovascular risk factors in MINOCA patients suggests alternative pathways that may contribute to the pathogenesis of myocardial ischemia. Diabetes mellitus is a major cardiovascular risk factor associated with worse prognosis and

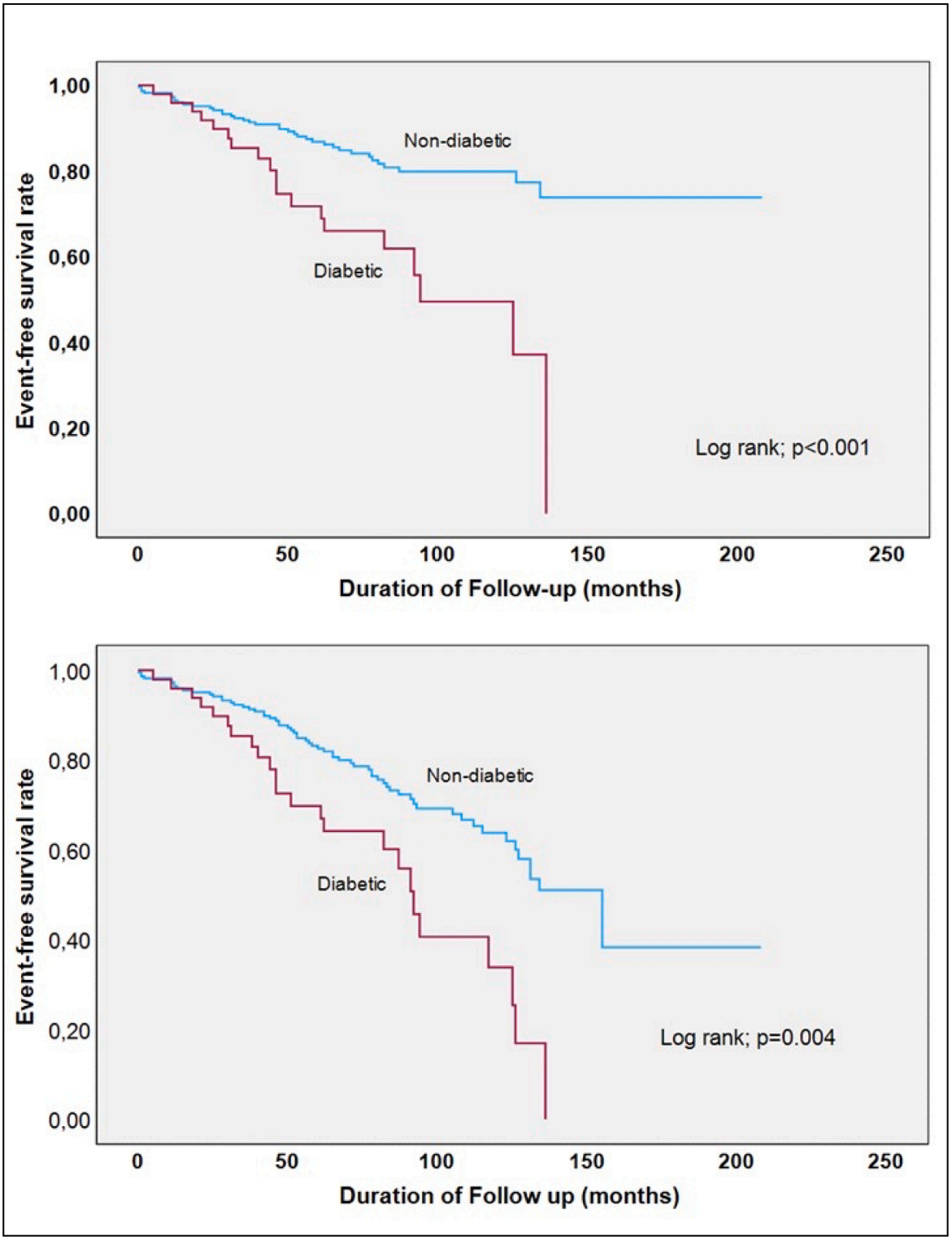

Fig. 2. Kaplan-Meier curves representing mortality (upper figure) and survival free from major adverse cardiac events (lower figure) during follow-up.

increased mortality rates [14]. Diabetes is a driving force in the development and progression of atherosclerosis, which manifests frequently in the coronary arteries [14]. Consequently, diabetes is strongly associated with obstructive CAD [3]. Previous studies have revealed that the incidence of diabetes and elevated glucose levels is significantly higher in patients with CAD than in MINOCA patients [13]. However, evidence on the role of diabetes in patients with MINOCA and on their outcome is limited.

In our analysis regarding baseline characteristics, diabetics were significantly more likely than non-diabetics to suffer from obesity, arterial hypertension, atrial fibrillation as well as neurological disease and kidney disease (Table 1). These findings are not surprising since obesity and arterial hypertension, together with diabetes mellitus, are part of the metabolic syndrome, and since cerebrovascular and renal diseases may be caused by micro- and macroangiopathy due to diabetes mellitus [14]. Similarly, atrial fibrillation is associated with diabetes as a

risk factor [15]. Notably, however, diabetics exhibited in our analysis lower creatine phosphokinase levels than nondiabetics. Troponin and BNP values as well as left ventricular ejection fraction, in contrast, were comparable between the groups. Moreover, diabetics presented higher serum thyroid-stimulating hormones than non-diabetics. Studies indicated that elevated TSH levels were associated with the occurrence of diabetes mellitus [16]. On the other hand, both low-normal and high-normal TSH levels could be associated with the occurrence of cardiovascular adverse events and mortality in patients with diabetes [17,18]. However, the median values of both groups were within the mid-normal range of values, neither low-normal nor high-normal (Table 1).

Furthermore, in-hospital follow-up revealed improved but similar left ventricular ejection fraction on echocardiography and distribution into heart failure groups (preserved/mildly reduced/reduced ejection fraction) in both groups (Supplemental Table 3).

As already evident in the baseline characteristics of the cohort, the results of the medication analysis confirmed that the diabetics had significantly more comorbidities, especially cardiovascular, than the nondiabetics. This was reflected in medication intake both at admission and discharge. Whereas the diabetics had pre-existing cardiovascular disorders, the non-diabetics received additional medications for secondary prevention of CAD, resulting in more similar prescription rates overall. Recently, an American study of 17,849 MINOCA patients demonstrated that there is substantial interhospital variability in the prescription of medications for secondary prophylaxis after myocardial ischemia [19]. Accordingly, angiotensin-converting enzyme inhibitors were prescribed in 16.0 % to 88.8 % and beta-blockers in 28.0 % to 97.5 % of MINOCA patients at discharge, suggesting that the routine use of these agents is clinically inconsistent [19]. The current European Society of Cardiology guidelines include only a brief statement that secondary prevention therapies should be considered in MINOCA patients for those in whom CAD has been detected and for further risk factor control [1]. There is limited evidence to date on the benefit of secondary prophylactic medication after MINOCA events, highlighting the urgent need for future randomized-controlled trials.

The in-hospital MACE rate as the primary study endpoint was slightly higher in diabetics (41.5 %) than in nondiabetics (33.9 %), but not statistically significant. Similarly, there were no significant differences in specific adverse events. In-hospital mortality was low with no deaths in diabetics and 2.9 % in non-diabetics (Supplemental Table 2).

In comparison, interestingly, diabetics experienced a significantly higher MACE rate during follow-up (51.9 % vs. 31.1 %). Noteworthy, diabetics also exhibited a significantly higher all-cause mortality rate than nondiabetics (42.3 % vs. 20.1 %). While there was no significant difference in cardiac-related deaths, non-cardiac deaths were more common in diabetics, although not statistically significant (Supplemental Table 4).

Our study suggests that while immediate cardiovascular complications during hospitalization might be comparable between diabetic and non-diabetic patients, a longer-term perspective reveals significantly higher rates of MACE and overall mortality among diabetics. Recent studies of MINOCA patients have identified older age, diabetes, insulin use, and chronic renal failure, among others, as predictors of MACE and increased mortality during follow-up [4,20,21]. The study by Gao et al. enrolled 1179 MINOCA patients who were categorized as normoglycemic, prediabetic, and diabetic based on HbA1c levels [22]. The primary endpoint, MACE, occurred more frequently in the prediabetes and diabetes groups than in the normoglycemic group, at a mean follow-up of 41.7 months [22]. After adjustment, both prediabetes and diabetes were independently associated with an increased risk of MACE [22]. Along with our findings, this underscores the importance of extended monitoring and enhanced outpatient care for diabetic patients to address their increased cardiovascular risks beyond the immediate hospitalization.

Overall, however, knowledge about the outcome of MINOCA patients and specifically the influence of risk factors on outcome is still limited. Our study indicated that the presence of diabetes, a major cardiovascular risk factor, in troponin-positive patients with non-obstructive CAD affects rather the long-term outcome than the short-term outcome. As diabetes mellitus is a chronic disease with various potential long-term effects, this is consistent with our findings [14]. In MINOCA patients, the absence of obstructive CAD, as otherwise often associated with coronary artery manifestations of atherosclerosis in diabetic patients [14], may indicate the presence of alternative pathways that may contribute to the pathogenesis of altered coronary arteries and consequently myocardial ischemia in these patients [23–26]. Chronic inflammatory processes, insulin resistance, and diabetes mellitus-promoted hypercoagulability could be possible pathophysiological pathways in MINOCA patients with diabetes mellitus [27,28]. In addition, diabetes-associated comorbidities such as obesity and arterial hypertension, as in our study cohort, are also associated with chronic inflammatory processes as a contributor to MACE [27,29,30]. In a study by Lopez-Pais et al., 109 patients with MINOCA were compared with 412 patients with myocardial infarction and obstructive CAD over a 3-year period [5]. MINOCA patients accounted for 16.9 % of total myocardial infarction admissions [5]. MINOCA patients were more likely to have proinflammatory conditions, which emerged as a risk factor for MINOCA in the predictor analysis [5]. In another large observational study, 9092 patients with MINOCA were examined [20]. During a mean follow-up of 4.5 years, the MACE rate was 24 % and the mortality rate was 14 % [20]. Interestingly, predictive factors for all-cause death included elevated CRP levels [20]. These findings may support the hypothesis that pro-inflammatory conditions, such as present in diabetes mellitus, may have an influence on the pathogenesis of MINOCA as well as the outcome.

5. Limitations

While our study provides valuable insights into troponin-positive patients with non-obstructive CAD with a particular focus on diabetes, it is important to consider the associated limitations. In addition to the retrospective nature of the study representing a key limitation, the cohort exhibits heterogeneity that may affect the generalizability of our findings. The inclusion of patients with a working diagnosis of MINOCA is a potential confounder. It is conceivable that patients may have received a definitive diagnosis during hospitalization, such as myocarditis or Tako-Tsubo syndrome, which was not considered in this analysis. The wide range of final diagnoses and dependent therapies within this subgroup may have influenced the observed results.

This study adopted a monocenter approach, which could have implications for medications prescribed at discharge. The limited scope of a single center raises questions regarding the generalizability of our findings to broader populations. In addition, the cohort size, particularly within the diabetes subgroup, is relatively small. This may lead to difficulty in detecting statistically significant differences, which could limit the power of some comparisons.

In addition, the lack of a control group with obstructive CAD is a notable limitation. Despite these limitations, this study is the first to focus exclusively on the role of diabetes and outcome in troponin-positive patients with non-obstructive CAD.

6. Conclusion

In conclusion, our study sheds light on the significant role that diabetes mellitus may play in the cardiovascular risk stratification of troponin-positive patients with non-obstructive CAD. The presence of diabetes mellitus emerges as a crucial factor in this cohort, emphasizing the need for tighter controls and strict adjustments due to the associated heightened mortality risk. Importantly, our findings suggest that the impact of diabetes on cardiovascular outcomes becomes more pronounced over a longer-term perspective, with elevated rates of both cardiovascular events and overall mortality. This revelation highlights

the intricate nature of cardiovascular disease in this unique subset of patients and calls for a paradigm shift in the understanding, diagnosis, and management of MINOCA across diverse populations. Tailored treatment strategies are important, involving targeting specific risk factors, optimizing lifestyle changes, and considering medications to effectively reduce the risk of future cardiovascular events.

CRediT authorship contribution statement

Fabienne Kreimer: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Clara Schlettert:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammad Abumayyaleh:** Writing – review & editing, Methodology, Conceptualization. **Ibrahim Akin:** Writing – review & editing, Validation, Conceptualization. **Mido Max Hijazi:** . **Nazha Hamdani:** Writing – review & editing, Software, Methodology. **Michael Gotzmann:** Writing – review & editing, Supervision. **Andreas Mügge:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Ibrahim El-Battrawy:** Writing – review & editing, Validation, Conceptualization. **Assem Aweimer:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101350.

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