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# Cardiac biomarkers but not measures of vascular atherosclerosis predict mortality in patients with peripheral artery disease

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ABSTRACT

*Background:* Peripheral artery disease (PAD) becomes more prevalent with advancing age and is associated with elevated risk of cardiovascular events and shortened life expectancy. We investigated the prognostic performance of cardiac and vascular biomarkers in a cohort of PAD patients.
*Methods:* A total of 95 PAD patients were enrolled (mean age 68 years, range 47 to 86 years, 73 males). Carotid intima-media thickness (cIMT), ankle brachial index (ABI), high sensitive cardiac troponin T, and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) were measured.
*Results:* During a median follow-up time of 9.5 years, 44 patients died and 51 patients survived. Upon Kaplan-Meier survival analysis hs-TnT ($P < .001$) or NT-proBNP levels ($P < .001$) above the median but not cIMT above the median ($P = .488$) or ABI below the median ($P < .436$)were associated with reduced survival rate. Upon univariate cox regression and after adjustment for age, gender, prior cerebral artery disease, and diabetes mellitus only the association between hs-cTnT and mortality remained significant (HR 1.93, 95% CI 1.33–2.79, $P < .001$). In receiver operating curve analysis hs-cTnT (area under the curve [AUC]: 0.77, 95% CI: 0.67–0.87, $P < .001$) NT-proBNP (AUC: 0.74, 95% CI: 0.64–0.84, $P < .001$) as well as hs-cTnT, and NT-proBNP combined (AUC: 0.79, 95% CI: 0.69–0.88, $P < .001$) were superior to cIMT (AUC: 0.64, 95%, CI: 0.53–0.76, $P = .022$) and ABI (AUC: 0.57, 95% CI: 0.44–0.68, $P = .313$) in discriminating risk for mortality.
*Conclusion:* hs-cTnT and NT-proBNP should be taken into account for prognosis of patients with PAD.

## 1. Introduction

The incidence of patients suffering from peripheral artery disease (PAD) amounts to 20% in the ageing population [1]. Apart from limiting quality of life, PAD is associated with a very high risk of cardiovascular events that amounts to 40% within three years [2]. For optimized and focused management it is important to stratify PAD patients by risk. However, it is difficult to differentiate high risk patients. Classical risk factors such as smoking, diabetes, hypertension, and hyperlipidemia have limited prognostic importance because they are frequently present in combination and treated. Biomarkers reflecting the presence and extent of disease may perform better. Carotid intima-media thickness (cIMT) for example is associated with vascular risk factors and the presence of atherosclerotic manifestations in other vascular beds including coronary artery disease [3]. Some studies also found cIMT to be an independent predictor for both cardiovascular and cerebrovascular events. cIMT was also used as surrogate end point for drug development in clinical trials, which however were discordant with clinical endpoints in several outcome-trials [4,5]. In addition, endothelial dysfunction assessed by brachial artery flow-mediated dilation represents an early precursor of atherosclerosis and was also shown an independent predictor of cardiovascular risk in patients with PAD [6]. Ankle brachial index (ABI) was described as a strong predictor of mortality in PAD patients [7].

*Abbreviations:* ABI, ankle brachial index; cIMT, carotid intima-media thickness; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-cTnT, high sensitive cardiac troponin T; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; PAD, peripheral artery disease; ROC, receiver operating characteristic

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Cardiac biomarkers such as N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) and high sensitive cardiac troponins were found to be significant prognostic biomarkers, which improve risk prediction by GRACE or TIMI scores in patients with stable coronary heart disease or acute coronary events [8–10] as well as risk prediction by Framingham risk and similar scores in asymptomatic individuals of the general population [11].

The prognostic value of imaging and cardiac markers in patients with PAD is less well investigated than in patients with coronary artery disease. We therefore compared the predictive values and interactions of cIMT, ABI as well as NT-proBNP and high sensitive cardiac troponin T (hs-cTnT) towards mortality in PAD patients.

## 2. Material and methods

### 2.1. Design

This prospectively performed single-centre study involved 95 PAD patients with an age range from 47 to 86 years (mean age: 68). 73 patients were males and 22 females. All patients were enrolled between 2002 and 2005 and followed for a period of ten years. We used the samples of patients that were included in a prior study, which included patients with angiographically or sonographically documented PAD of the lower extremities, with or without a history of peripheral vascular intervention or vascular surgery, were eligible and were consecutively recruited from PAD patients who had regular consultation at our clinic of angiology. The severity of PAD at the time of enrollment was classified according to Rutherford. Only patients with Rutherford category 0 to 3 (corresponding to Fontaine stages I and II) were eligible [12].

This study was performed in line with the principles of the Declaration of Helsinki and after obtaining approval from the Cantonal Ethics Committee of Zurich. In addition, written informed consent was obtained from all patients at baseline after proper explanation of the study and its purpose to the patients.

### 2.2. Non-laboratory tests

Baseline characteristics included patients' age, sex, and vascular risk factors. Diabetes was defined as fasting serum glucose ≥7 mmol/l or use of oral antidiabetics or insulin. Hyperlipidemia was defined as use of lipid-lowering drugs or total cholesterol > 5.17 mmol/l and/or triglycerides > 2.26 mmol/l. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg. Smoking was defined as active cigarette smoking. Body mass index was calculated as weight in kilograms divided by height in meters squared. Patients were asked and their charts reviewed for manifestations of coronary heart disease and cerebrovascular events. ABI measurements were performed (an ABI < 0.9 indicating arterial obstruction and > 1.3 indicating media calcinosis). The ABI was measured with the patient lying in the supine position. Blood pressure measurements of both brachial arteries as well as the dorsalis pedis and posterior tibial arteries in the foot were performed, using a standard hand-held Doppler probe for the foot arteries. The blood pressure cuff was inflated until no arterial signal could be heard and then slowly deflated until the Doppler signal reappeared. The ABI-value was calculated by taking the higher pressure of the arteries at the ankle, divided by the brachial arterial systolic pressure.

The intima-media thickness of the common carotid artery was measured from high-resolution ultrasound images acquired by a linear array transducer (GE Logiq 9). Intima-media thickness was defined as the distance between the leading edges of the lumen interface and the media-adventitia interface of the far wall.

### 2.3. Laboratory tests

All analyses were performed by the Institute of Clinical Chemistry on plasma samples that were isolated from blood samples taken at recruitment between 2002 and 2005. The Friedewald equation was used for calculating LDL-cholesterol. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for estimating the glomerular filtration rate (eGFR). hs-cTnT and NT-proBNP were analysed in plasma samples which were kept frozen at −80 °C in a biobank. NT-proBNP and hs-cTnT were measured by the use of electrochemiluminiscence immunoassays and an e601 analyser of COBAS 8000 from Roche diagnostics (Rotkreuz, Switzerland).

### 2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, NY), GraphPad Prism version 5.04 (GraphPad Software Inc., San Diego, CA) and Analyse-it for Microsoft Excel version 4.65.3 (Analyse-it Software Ltd., Leeds, UK). Categorical variables are presented as numbers (percentages) and compared between groups using the chi-square test. Continuous variables are presented as mean ± standard deviation or medians with 25th and 75th percentiles and compared between groups using the student's *t*-test or Mann-Whitney *U* test as appropriate.

To evaluate the association of cIMT, ABI, hs-cTnT, and NT-proBNP with mortality during follow-up, Kaplan-Meier curves of cIMT, ABI, hs-cTnT, and NT-proBNP above and below the median were plotted. Survival curves of two groups were compared for significance using log-rank test.

Hazard ratios (HRs) and 95% confidence intervals (Cis) for mortality were calculated using univariate and multivariate Cox proportional hazard regression analysis models. In multivariate analyses, the associations were adjusted for age and gender (model 2) and age, gender, prior cerebral artery disease, and diabetes mellitus (model 3).

A $P$ value < .05 was considered to indicate statistical significance.

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive capacity of cIMT, ABI, hs-cTnT, and NT-proBNP for mortality in PAD patients. The area under the ROC curve (AUC) as well as the 95% CIs was computed and the optimal thresholds with maximum combination of sensitivity and specificity in predicting mortality determined.

## 3. Results

95 patients were enrolled at baseline between 2002 and 2005. 51 of these patients were alive and 44 of these patients were dead at follow-up in 2016. The PAD patients that died during follow-up were older, had a higher prevalence of diabetes mellitus and more often had a positive history of cerebral artery disease than the PAD patients that survived (Table 1). More male patients were included in the study. The higher prevalence of male patients in our cohort might be explained by the fact that most patients are referred due to symptomatic PAD and symptoms seem to be more severe in men [13]. The cIMT was slightly higher in patients that died than patients that survived during follow-up (median: 0.78, range: 0.62–1.16 mm vs. median: 0.76 mm, range: 0.48–1.05 mm; $P$ = .002; Fig. 1A), whereas no differences were observed between the two groups with respect to ABI (median: 0.79, range: 0.42–1.28 for survivors vs. median: 0.84, range: 0.47–1.48 for non-survivors; $P$ = .486; Fig. 1B). A comparison of cardiac biomarkers between survivors and non-survivors showed that non-survivors had significantly higher levels of hs-cTnT (median: 15 ng/l, range: 4–66 ng/l vs. median: 7 ng/l, range: 3–26 ng/l; $P$ < .001; Fig. 1C) and NT-proBNP (median: 439 ng/l, range 55–7093 ng/l vs. median: 120 ng/l, range: 14–1258 ng/l; $P$ < .001; Fig. 1D) than survivors.

Kaplan-Meier curves were constructed for survival during follow-up, with PAD patients categorized in two groups based on median levels of cIMT, ABI, hs-cTnT, and NT-proBNP. There was no significant difference in cumulative survival between PAD patients with cIMT values above and below the median ($P$ = .488; Fig. 2A) or between PAD

**Table 1**
Baseline characteristics of the study participants by survival status at follow-up.

| | Survivors | Non-survivors | *P*-value |
|---|---|---|---|
| | (*n* = 51) | (*n* = 44) | |
| Demographics | | | |
| Age, years | 65.8 ± 9.6 | 71.1 ± 9.1 | 0.007 |
| Male, *n* (%) | 39 (77%) | 34 (77%) | 0.926 |
| Vascular risk factors | | | |
| Body mass index, kg/m$^2$ | 25.0 [22.3–27.6] | 25.1 [22.2–29.0] | 0.380 |
| Current smoking, *n* (%) | 26 (51%) | 25 (57%) | 0.569 |
| Hypertension, *n* (%) | 42 (82%) | 35 (80%) | 0.728 |
| Diabetes mellitus, *n* (%) | 10 (20%) | 20 (46%) | 0.007 |
| Hyperlipidemia, *n* (%) | 38 (75%) | 34 (77%) | 0.754 |
| Prior myocardial infarction, *n* (%) | 13 (26%) | 9 (21%) | 0.562 |
| Prior cerebral arterial disease, *n* (%) | 19 (37%) | 26 (59%) | 0.034 |
| Prior stroke, *n* (%) | 2 (4%) | 1 (2%) | 0.647 |
| Lipids | | | |
| Cholesterol, mmol/l | 4.57 ± 1.09 | 4.30 ± 0.83 | 0.189 |
| LDL-cholesterol, mmol/l | 2.82 ± 1.31 | 2.63 ± 0.82 | 0.608 |
| HDL-cholesterol, mmol/l | 1.33 ± 0.40 | 1.24 ± 0.33 | 0.276 |
| Triglycerides, mmol/l | 1.69 [1.21–2.57] | 1.78 [1.08–2.52] | 0.826 |
| Inflammation | | | |
| CRP, mg/l | 3.1 [1.3–5.6] | 3.7 [1.7–6.7] | 0.335 |
| Renal function | | | |
| eGFR, ml/min/1.73 m$^2$ | 69.5 ± 19.8 | 63.4 ± 21.8 | 0.157 |

Normally distributed continuous variables are presented as mean ± SD, continuous variables with a skewed distribution are presented as median [25th–75th percentile], and categorical data are summarized by n (%). Differences were tested with student's *t*-test or Mann-Whitney *U* test for continuous variables and chi-square test for categorical data.
CRP = C-reactive protein, eGFR = estimated glomerular filtration, HDL = high-density lipoprotein, and LDL = low-density lipoprotein.

patients with ABI values above and below the median ($P = .436$; Fig. 2B). However, the cumulative survival rate was significantly lower in PAD patients with baseline hs-cTnT levels above the median of 9 ng/l ($P < .001$; Fig. 2C). Likewise, NT-proBNP levels above the median were associated with a higher incidence of death in PAD patients ($P < .001$; Fig. 2D).

Univariate and multivariable cox regression analyses for mortality with the traditional risk factors cIMT and ABI as well as the cardiac markers hs-cTnT and NT-proBNP were performed (Table 2). ABI at baseline was not associated with mortality during follow-up in PAD patients in both univariate (HR: 1.15, 95% CI: 0.81–1.63, $P = .435$) and multivariate analyses (Table 2, model 2–3). In unadjusted analyses, a 1-SD increase in cIMT was associated with a hazard ratio of 1.68 for mortality (95% CI: 1.14–2.47, $P = .008$), but after adjustment for age and gender this association disappeared (Table 2, model 2). In contrast, there was an elevated risk for death with an increase in hs-cTnT (unadjusted HR: 2.30, 95% CI: 1.71–3.09, $P < .001$) and NT-proBNP (unadjusted HR: 1.36, 95% CI: 1.13–1.63, $P < .001$) levels at baseline that remained significant after adjusting for age and gender (Table 2, model 2). However, following adjustment of differences in baseline characteristics (model 3), i.e. age, gender, prior cerebral artery disease, and diabetes mellitus, only hs-cTnT remained as a significant independent predictor of mortality with an hazard ratio of 1.93 (95% CI, 1.33–2.79, $P < .001$; Table 2, model 3).

ROC curves were used to compare the prognostic ability of the different biomarkers. (Fig. 3). Based on the AUC, hs-cTnT was the best predictor of mortality in PAD patients during follow-up (AUC: 0.77, 95% CI: 0.67–0.87; $P < .001$), followed closely by NT-proBNP (AUC: 0.74, 95% CI: 0.64–0.84; $P < .001$). The optimal cut-off value of hs-cTnT for predicting mortality in PAD patients was 9 ng/l with 68.2% sensitivity and 72.5% specificity. The best cut-off value of NT-proBNP of 159 ng/l predicted mortality with a sensitivity of 70.5% and a

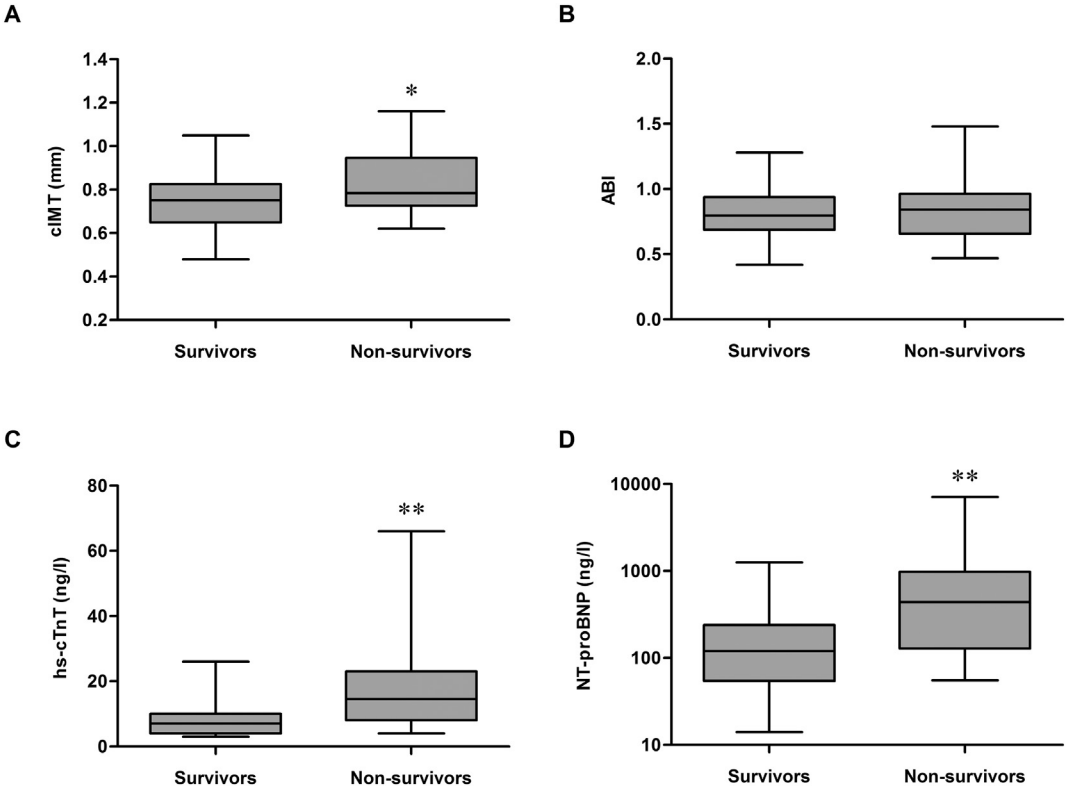


**Fig. 1.** Box-plots demonstrating baseline (A) carotid intima-media thickness (cIMT) levels, (B) ankle-brachial index (ABI) values, (C) high-sensitivity cardiac troponin T (hs-cTnT) levels, and (D) N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) levels in patients with peripheral artery disease according to survival status. The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the line in the middle represents the median. The whiskers represent the highest and lowest values. *$P < .01$, **$P < .001$.

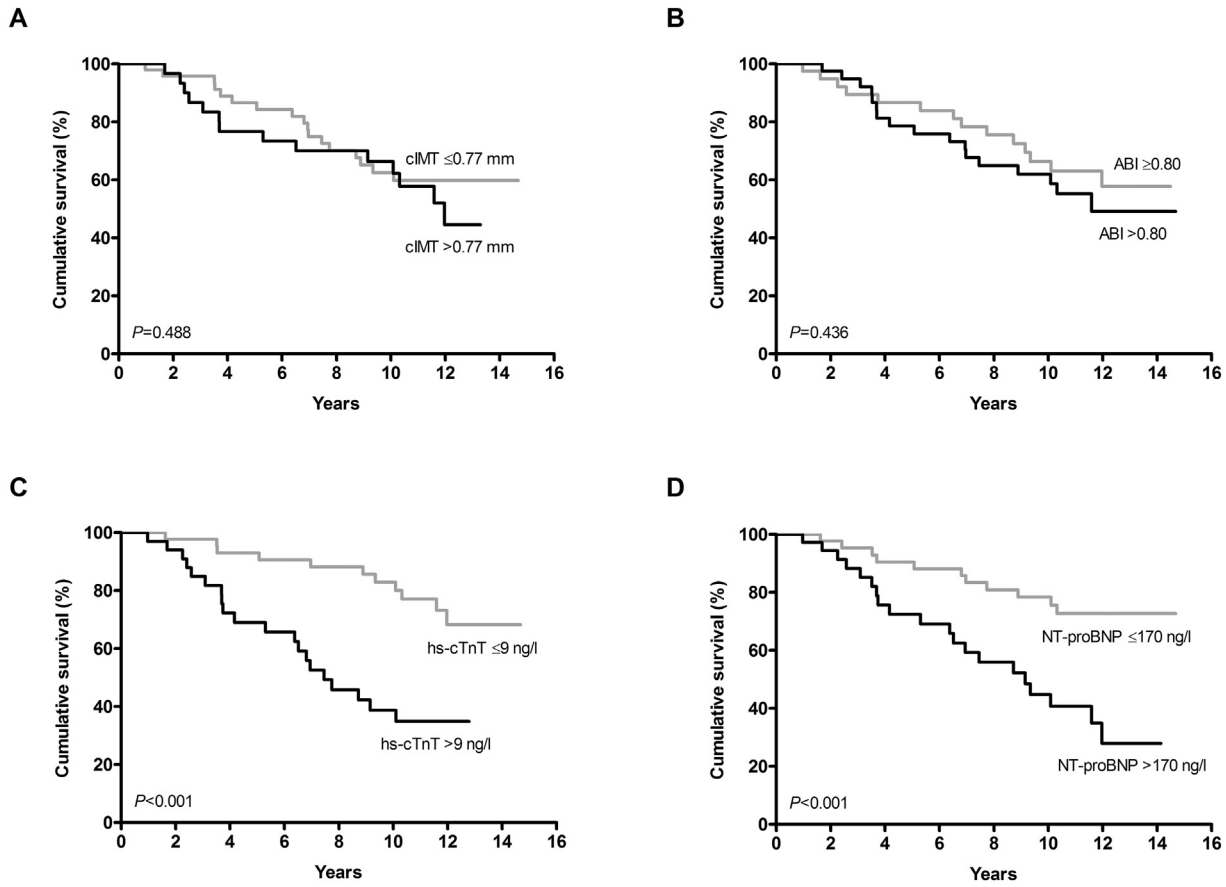


**Fig. 2.** Kaplan-Meier survival curves and log rank tests according to median levels of (A) carotid intima-media thickness (cIMT), (B) ankle-brachial index (ABI), (C) high-sensitivity cardiac troponin T (hs-cTnT), and (D) N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) in patients with peripheral artery disease. For 18 non-survivors no date of death was available.

**Table 2**
Cox regression analysis for the association of carotid intima-media thickness (cIMT), ankle-brachial index (ABI), high-sensitivity cardiac Troponin T (hs-cTnT) and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) with mortality in patients with peripheral artery disease.

| | cIMT | | ABI | | hs-cTNT | | NT-proBNP | |
|---|---|---|---|---|---|---|---|---|
| | HR per 1SD increase (95% CI) | *P*-value | HR per 1SD increase (95% CI) | *P*-value | HR per 1SD increase (95% CI) | *P*-value | HR per 1SD increase (95% CI) | *P*-value |
| Model 1 | 1.68 [1.14–2.47] | 0.008 | 1.15 [0.81–1.63] | 0.435 | 2.30 [1.71–3.09] | < 0.001 | 1.36 [1.13–1.63] | < 0.001 |
| Model 2 | 1.32 [0.84–2.06] | 0.234 | 1.10 [0.76–1.58] | 0.630 | 2.02 [1.44–2.84] | < 0.001 | 1.24 [1.02–1.50] | 0.031 |
| Model 3 | 1.27 [0.81–1.98] | 0.293 | 0.94 [0.66–1.34] | 0.734 | 1.93 [1.33–2.79] | < 0.001 | 1.15 [0.94–1.42] | 0.179 |

Model 1: crude model.
Model 2: adjusted for age and gender.
Model 3: adjusted for age, gender, prior cerebral artery disease and diabetes mellitus.
HR = hazard ratio, SD = standard deviation, CI = confidence interval.

specificity of 64.7%. The combination of hs-cTnT and NT-proBNP did improve the prognostic accuracy for mortality (AUC: 0.79, 95% CI: 0.69–0.88; $P < .001$) as compared to hs-cTnT or NT-proBNP alone. In addition, also the cIMT was a predictor of mortality in our cohort of PAD patients, with an optimal threshold of 0.77 mm (sensitivity 53.5%, specificity 56.3%). However, the AUC for cIMT of 0.64 (95% CI: 0.53–0.76; $P = .022$) was considerably lower than the AUC of hs-cTnT or NT-proBNP. ABI did not demonstrate a significant predictive value for mortality with an AUC of 0.56 (95% CI: 0.44–0.68, $P = .313$).

With regard to CRP, we found no significant difference in levels of this inflammatory marker in deceased PAD patients as compared to survivors. Moreover, our current work in PAD patients could not detect an association between baseline CRP levels and all-cause mortality during follow-up (see Table 3).

## 4. Discussion

Peripheral artery disease (PAD) is common in elderly people and associated with an elevated risk of cardiovascular events and shortened life expectancy [14]. Most of these patients have polyvascular disease and exhibit a cardiovascular event rate of 40% within three years [2]. Improving therapies save more patients from dying from cardiovascular events, so that nowadays more patients with PAD seem to die of neoplasms [15].

Traditional markers used to measure the severity of PAD are ABI and cIMT. However, it is still difficult to predict cardiovascular events or mortality in patients suffering from PAD that only suffer from an intermediately impaired arterial perfusion of the lower legs. While a severely reduced ABI (< 0.4) seems to be a reliable parameter for the

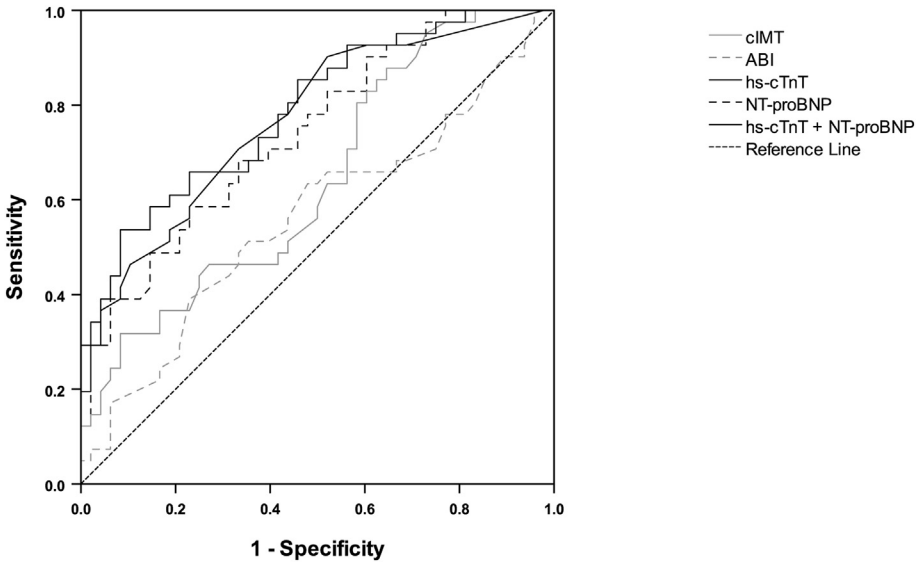


**Fig. 3.** Receiver operating characteristic (ROC) curves of carotid intima-media thickness (cIMT), ankle-brachial index (ABI) and the cardiac markers high-sensitivity cardiac troponin T (hs-cTnT), and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) for the prediction of mortality in patients with peripheral artery disease. The dashed line represents the reference line.

**Table 3**
Cox regression analysis for the association of C-reactive protein with mortality in patients with peripheral artery disease.

| | CRP | |
|---|---|---|
| | HR per 1SD increase (95% CI) | *P*-value |
| Model 1 | 0.99 (0.55–1.77) | 0.961 |
| Model 2 | 1.16 (0.64–2.12) | 0.625 |
| Model 3 | 1.10 (0.60–2.04) | 0.754 |

Model 1: crude model.
Model 2: adjusted for age and gender.
Model 3: adjusted for age, gender, prior cerebral artery disease and diabetes mellitus.
HR = hazard ratio, SD = standard deviation, CI = confidence interval.

prediction of deceasing, the reliability of cIMT as commonly used predictor of cardiovascular events is under discussion. Other biomarkers that are additionally able to identify PAD patients at high risk for fatal outcome are needed. Otaki et al. could also show, that the myocardial damage markers H-FABP and hs-cTnT were increased in PAD patients with CLI and could predict major adverse cardiovascular events such as cardiovascular and cerebrovascular diseases and amputations [16]. They also named these markers of latent myocardial damage as promising markers for early detection of PAD patients at high risk for major cardiovascular and cerebrovascular events. Additionally, the present study investigated the predictive value of the hs-cTnT and NT-proBNP for mortality and compared the predictive power of these cardiac markers with the traditional markers ABI and cIMT.

NT-proBNP for example is a well-established biomarker in heart failure. NT-proBNP blood levels reflect cardiac function and are used for the rule out of acute congestive heart failure and left ventricular dysfunction [17]. Moreover, high levels of NT-proBNP predict worse outcome in patients with acute or chronic heart failure [18] as well as in patients with acute coronary syndrome, stable coronary heart disease, acute ischemic stroke, or even asymptomatic individuals [19–25]. The data in our cohort indicate the prognostic value of NT-proBNP also in patients with PAD. PAD patients that survived during follow-up had lower NT-proBNP levels and levels above the median were associated with a higher incidence of death. A NT-proBNP-level of 159 ng/l was the best cut-off value with a sensitivity of 70.5% and a specificity of 64.7% to predict mortality in our cohort. As no adequate data on cardiac function of patients in our cohort was available, especially not the ejection fraction (EF), we were not able to correlate NT-proBNP-levels to the EF. Screening for heart failure in PAD patients with assessment of NT-proBNP-levels and echocardiography is recommend in the 2017 ESC guidelines on the Diagnosis and Treatment of Peripheral Arterial Disease [14].

Hs-cTnT is a well-established biomarker of myocardial ischemia and subsequent necrosis that is primarily used for the rule out and rule-in of acute myocardial infarction in acute coronary syndrome. Like NT-proBNP it is also shown to predict poor outcome in patients with acute coronary syndrome, stable CAD, or heart failure as well as in asymptomatic individuals [26]. Similar to elevated NT-proBNP, we found that elevated hs-cTnT in PAD patients was associated with death. In the current study, hs-cTnT concentrations were increased in non-survivors and survival rates were lower in PAD patients with hs-cTnT levels above the median. Moreover, hs-cTnT was the only independent predictor of all-cause mortality. A hs-cTnT value above 9 ng/l was identified as the cut-off value that best predicted mortality in PAD patients with a sensitivity and specificity of 68.2% and 72.5%, respectively.

Interestingly in our study, more direct measures of peripheral atherosclerosis, did not predict mortality either at all (ABI) or independently of confounders (cIMT). Our negative finding is in discordance with some previous studies, which found that ABI associated with poor outcome in patients with PAD [27,28]. However, many recently published studies have also questioned the predictive value of cIMT and ABI [29,30]. The patients in our cohort did not have ABI below 0.4, and only few an ABI below 0.5, indicating a severe PAD that is associated with poor outcome and shortening of life. This might explain the difference of findings in our cohort compared to other studies that described an ABI below 0.4 or 0.5 as strong predictor of mortality [31]. Another recent study describes ABI as predictor for cardiovascular events, but did also not discriminate between intermediate and severe PAD based on the ABI [15]. CRP-levels, as inflammatory marker, were also compared in deceased patients and survivors, but did not show any significance. Possibly, the sample size of our study was too small to identify CRP as an independent predictor of poor outcome. Another potential explanation for the lack of a predictive value of CRP for mortality in this study might be that we studied all-cause mortality and not mortality due to major cardiovascular events. As no data on the cause of death are available for the current study, we are not able to perform analysis specifically for cardiovascular mortality. It is not unequivocally established that CRP is a valid predictor of cardiovascular events in PAD patients. While a meta-analysis including 8 studies did indicate that higher CRP concentrations are associated with a higher risk of major cardiovascular events [32], other studies have not found a significant predictive value of CRP in identifying PAD patients at risk of

long-term fatal cardiovascular events [33,34].

Matsushita et al. could show that high-sensitivity cTnT and NT-proBNP were independently associated with incident peripheral arterial disease and particularly its severe form, the chronic critical limb ischemia (CLI) which lead also to the conclusion that these markers should be taken into account for prognosis of patients with PAD. They defined CLI as indicative of rest leg pain, ulcer, and gangrene, which is in accordance with actual guidelines [14], but did not measure the ABI [35].

In summary, knowing that patients with PAD with low ABIs have a high risk of deceasing, the present data suggests, that patients with ABIs that are only intermediately decreased have a higher risk of deceasing when hs-cTnT and NT-proBNP are elevated. Therefore, these markers should be taken into account when stratifying the individual risk of cardiovascular events and death in patients with PAD.

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