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Development of a 3-dimensional prognostic score for patients with symptomatic peripheral artery disease – PAD^{3D} Score

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Abstract

Peripheral artery disease (PAD) is a high-risk condition for cardiovascular (CV) events but no specific prognosis assessment tool exists. We developed an individual risk score (PAD^{3D}) based on the combined predictive value for mortality that includes: (i) age, (ii) severity of PAD, and, (iii) extent of atherosclerosis. Patients (n=1310) with symptomatic PAD were followed-up for a mean of 50 ± 26 months. The cohort was randomly subdivided into a test and validation cohort. All-cause and CV mortality were prospectively analyzed for PAD^{3D} score and in combination with classical risk factors. For the test and validation cohort (n=655 each), all-cause and CV mortality was predicted ($p<0.001$) by the PAD^{3D} score. Additional inclusion of classical risk factors did not increase discrimination compared with PAD^{3D} as "Area-Under-Receiver-Operating-Characteristic" (AU-ROCs) curves were similar for both scores at any time point. Thus, the addition of the classical risk factors to PAD^{3D} did not further improve the prognostic value. The PAD^{3D} score provides a risk gradient of a 4.5-fold increase in all-cause and CV mortality. We developed a score for precise prediction of all-cause and CV mortality. The PAD^{3D} score promises to allow for personalized goals in risk intervention.

Keywords: peripheral artery disease; cardiovascular outcome; prognostic score; risk quantification; test and validation cohort; personalized medicine;

Abbreviations:

ABI	ankle brachial index
AU-ROC	Area-Under-Receiver-Operating-Characteristic
ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
CHA_2DS_2VASC	**C**ongestive heart failure-**H**ypertension-**A**ge-**D**iabetes-**S**troke-**V**ascular Disease-**A**ge-**S**ex **c**ategory
CLI	critical limb ischemia
CeVD	cerebrovascular disease
CV	cardiovascular
IC	intermittent claudication
LDL-C	low density lipoprotein cholesterol
PAD	peripheral artery disease
PAD^{3D}	peripheral artery disease 3-dimensional risk score
PAD^{RF}	classical PAD risk factors

Introduction

For chronic progressive diseases, a contemporary approach is to tailor preventive therapy to the magnitude of risk. The higher the absolute global risk, the more aggressive the risk intervention should be.[1-3] A good example is atherosclerotic cardiovascular disease (ASCVD), where recommendations, e.g. for low density lipoprotein cholesterol (LDL-C) classical lowering treatment,[4] adhere to this rule. It is widely accepted that patients with very high risk deserve the most intensive risk-reducing therapy.[1, 2, 5-8]

The prediction of a risk level relies on observational epidemiology. Risk factors predict initiation of disease. However, this approach, while useful at the population level, is currently under challenge as a tool to assess risk for disease progression in individuals with established disease [for review see [9]]. It is therefore under debate whether risk factors are useful to predict disease progression over and above disease initiation. One important limitation is that risk factors are treated, which means that their predictive value in risk assessment is weakened.

Hence, there is a need for a more specific prediction of prognosis like the Congestive heart failure-Hypertension-Age-Diabetes-Stroke-Vascular Disease-Age-Sex category (CHA_2DS_2VASC) score for risk prediction of embolism in atrial fibrillation.[10] For ASCVD, scores exist for risk prediction in coronary artery disease.[11, 12] Within the spectrum of ASCVD, one entity with very high risk is peripheral artery disease (PAD).[1, 2, 13-17] However, clinical experience suggests that PAD has a wide range of prognosis and the “one-size-fits-all” approach is an approximate and insensitive one.[18] Surprisingly, there is no well-defined, specific risk score for patients with symptomatic PAD.

It is well known that the severity of PAD, as defined by reported symptoms,[18] or by the level of the ankle brachial index (ABI),[19, 20] determines cardiovascular outcome. Moreover, from observational studies, there is evidence that presence of polyvascular atherosclerosis, besides age, increases event rates.[21-24] We therefore aimed at developing a risk score from prospective observational data of a large cohort of symptomatic PAD patients considering age, severity of PAD and polyvascular extent of atherosclerosis, i.e. clinically easily identifiable characteristics. We tested the hypothesis that - in a patient with symptomatic PAD, (i) age, (ii) severity of PAD, defined by the Rutherford classification, and, (iii) polyvascular extent of atherosclerosis provide a comprehensive estimate of the individual's future risk for all-cause and cardiovascular mortality, first in a test cohort and then in a validation cohort for verification. Also, we compared the prognostic value of this score with that of classical risk factors.

Patients and methods

Study design

A consecutive sample of 1343 patients with symptomatic PAD from the institutional database of patients undergoing angioplasty being referred to the Swiss Cardiovascular Center between 2010 and 2017, were identified as eligible for analysis. Thirty-three individuals refused participation, leaving 1310 patients for outcome analysis. The database and participant informed consent form were approved by the Swiss Ethics Committee on research involving humans. Each written informed consent was obtained prior to inclusion according to the declaration of Helsinki.

We first established the single prognostic value of each putative predictor. Based on their hazard ratios we then developed a comprehensive prognostic score (PAD^{3D}) for our patient population with symptomatic PAD in a test cohort. Next, we evaluated the performance of this score in a validation cohort. We added the information on classical risk factors to a more comprehensive score of PAD^{3D} plus risk factors (PAD^{RF}) and again investigated its value in a test cohort as well as in a validation cohort.

Intermittent claudication (IC) was defined as a symptomatic deficiency in blood supply to exercising muscle relieved during resting classified by the Rutherford class 1 (mild claudication), 2 (moderate claudication) and 3 (severe claudication).[25] Critical limb ischemia (CLI) was defined according to the Second European Consensus Document.[26] CLI represents persistently recurring ischemic rest pain or ulceration or gangrene of the foot or toe associated with an ankle systolic pressure ≤50 mmHg or a toe systolic pressure

of ≤30 mmHg or both, and is classified as Rutherford category 4 (rest pain) or 5 or 6 (minimal (class 5) or major (class 6) ulceration).[25]

Consistent with our study aims to provide a practically useful tool, we selected clinical parameters with potential prognostic value. Thus, to assess the risk profile of our patients we recorded: (i) age, (ii) severity of PAD, defined by the Rutherford classification, and, (iii) extent of ASCVD in the 3 vascular beds, i.e. coronary, cerebrovascular and peripheral, based on the patient's medical history as documented in their medical records.

Inclusion and exclusion criteria

All patients enrolled into the study suffered from symptomatic PAD in Rutherford category 1-6 due to atherosclerotic disease. All were admitted for angiography and underwent endovascular revascularisation within 24 h after acquisition of the baseline clinical and laboratory data. Patients with acute onset (<14 days) or documented arterial or cardiac embolism were excluded, as well as patients below the age of 40 years, since these patients most likely suffer from arterial diseases other than ASCVD.

End Points

Information on all-cause mortality, cardiovascular death, were obtained from the hospital's medical information system (iPDOS). Cardiovascular death was defined as any death related to a cardiovascular or limb event, i.e. myocardial infarction (i.e. ST-elevation myocardial infarction or non-ST elevation myocardial infarction (STEMI, NSTEMI, respectively), coronary artery bypass graft (CABG) surgery, cerebrovascular stroke, transient ischemic attack (TIA), carotid surgery or angioplasty or peripheral bypass surgery or transluminal angioplasty of the lower limbs.

PAD^{3D} Score

For the establishment of the 3-dimensional PAD score (PAD^{3D}), we set up a ranking scale using age (dimension 1) by introducing cut-offs according to clinical conventions, severity of PAD according to Rutherford classification (dimension 2) and polyvascular extent of atherosclerosis apart from PAD (dimension 3) (see table 2 for details).

For the weighting of the 3 dimensions of the score, we used the observed results of the survival data from our test population. For each single dimension, we calculated Hazard Ratios (HR) from the relative mortality rates. We then transformed the HR into score points, which were rounded up or down to the next integer. Thus, we then weighted the baseline age as well as severity and extent of disease. The PAD^{3D} score was then a simple sum of the points obtained from the 3 single dimensions. To construct PAD^{RF}, we added information of classical risk factors (other than age): hypertension, diabetes mellitus, smoking, dyslipidemia as well as gender. Each risk factor was weighted regarding the survival data, from which we calculated the HR. The HR was again transformed into score points, rounded to the next whole number. The PAD^{RF} score was a simple sum of the points from the risk factors added to the PAD^{3D} score.

In order to evaluate the validity of the scores found in the test cohort, we applied the score to a validation cohort of equal size. This approach was used for the PAD^{3D} score, first without and then with risk factor inclusion. Table 2 shows a listing of the points distributed for both scores.

PAD^{3D}/ PAD^{RF} Statistical analysis

Analyses were performed using the GraphPad Prism© statistical software package, version 7.0c (GraphPad®, San Diego, CA, USA) or Stata 14 (Stata Corp. LLC, College Station, TX, USA). We validated the scores by calculating sensitivity, specificity and post-test probability at each level, plotted receiver operating characteristic (ROC) curves and compared areas under the ROC curves (AUROCs), using the entire study cohort.

Categorical data are presented as absolute numbers and percentages. The distributions of metrical variables are presented as means with standard deviations (SD). Kaplan-Meier survival analysis was used to estimate all-cause and cardiovascular mortality using log rank test, being reported with the 95% confidence interval (CI). A two-sided $p<0.05$ was considered significant.

Results

Patient characteristics

Demographic and laboratory data of patients are shown in Table 1. Prevalence of cardiovascular risk factors in the study population was high, with nearly two thirds being active smokers, and one third had diabetes mellitus. Hypertension was the most common risk factor (85.3%). Two thirds of the patients had IC (Rutherford 1 - 3), one third presented with CLI (Rutherford 4 - 6) at the time of referral. For detailed data of the test cohort as well as of the validation cohort see Table 1.

Survival data of the test cohort

Overall, we recorded a total of 234 deaths, including 91 documented deaths from cardiovascular causes. Supplemental table 1 lists the different causes of cardiovascular deaths. Kaplan Meier survival curves for age strata are presented in supplemental Figure S1.

Figure S2 depicts Kaplan Meier survival curves according to the severity of PAD as assessed by the Rutherford classification. All-cause mortality as well as cardiovascular mortality were significantly higher in more severe stages.

Figure S3 describes the all-cause and cardiovascular mortality as well as the event rate depending of the polyvascular extent of atherosclerosis. Extent was significantly predictive of all-cause and cardiovascular mortality.

For the test cohort we further analyzed the survival data for classic risk factors. These are presented in the supplemental Figures S4 (gender), S5 (hypertension), S6 (diabetes mellitus), S7 (smoking) and S8 (dyslipidemia).

Calculation of the PAD^{3D} Score

The mortality data of the 3 dimensions age (Figure S1), severity of PAD (Figure S2) and extent of atherosclerosis (Figure S3) allowed for weighting of each dimension as determined by the calculated HR. In detail, age between 65 and 75 years scored 1 point and 2 points above 75 years. Rutherford class 1 and 2 scored 1 point, Rutherford class 3 scored 2 points, and critical stages according to Rutherford class 4, 5 and 6 scored 3 points for class 4, and 4 points for class 5 and 6, respectively. The extent of atherosclerosis apart from PAD scored 1 point for cerebrovascular disease (CeVD), 3 points for coronary artery disease (CAD) and 6 points for polyvascular disease (PV), i.e. CeVD and CAD combined. The numerical contribution of components of the PAD^{3D} score are listed in Table 2. Similarly, the weighting of the risk factors – hypertension, smoking, diabetes mellitus, dyslipidemia and gender – was determined by the calculated HR. These points were added to the PAD^{3D} score, now referred to as PAD^{RF} score. The numerical contribution of components of the PAD^{3D} score, as well as of the PAD^{RF} score are listed in Table 2.

Outcome in relation to the PAD^{3D} Score in the validation cohort

Figure 1 shows the Kaplan-Meier curves for all-cause and cardiovascular mortality in relation to the PAD^{3D} score as defined. The score precisely predicts all outcome levels. In Figure 2 the mortality rates are presented along the 3 score groups.

These data demonstrate that there is a wide variation of outcomes among patients with symptomatic PAD. For example, all-cause mortality in the highest score group was 36 *vs* 8% in the lowest score group; cardiovascular mortality was 23 *vs* 5%, respectively. This means that there is nearly a 5-fold increased mortality along the scoring of this population of symptomatic PAD patients. Specifically, a PAD^{3D} of 6 or higher is associated with increased risk of 1-year all-cause mortality by 2, from 7 to 14%. If PAD^{3D} is as high as 10, the risk of 1-year mortality is 30% (Suppl. Table 2 a).

The inclusion of classical risk factors did not increase discrimination compared with the PAD^{3D} score alone as AUROCs were similar for both scores at 1 and 2 years, as well as at any other time point (Fig. 3; Suppl. Table 2b, Suppl. Fig. 10). Fig. 1 and 2 show corresponding Kaplan-Meier curves and bar charts, respectively, for the validation cohort. Furthermore, the difference between moderate and high-risk strata virtually disappeared for both, all-cause and CV mortality. All-cause mortality amounted to 30% in the highest risk group *vs* 8% in the lowest risk group, i.e. 3.75 fold; and CV mortality to 13 *vs* 6%, i.e. 2.2 fold, respectively. Increased PAD^{RF} is in general not associated with increased risk of mortality as post-test probability drops for high scores (see in Supplemental table 2a right hand side).

Discussion

This prospective study of a large cohort of patients with symptomatic PAD had three aims. First, we established the relation between outcome and age, severity of PAD, as well as polyvascular atherosclerotic extent in a test cohort. Second, we developed a score to estimate mortality risk of an individual patient with symptomatic PAD and, third, used this PAD^{3D} score to verify its prognostic power in a validation cohort. This novel score proved very useful to estimate the prognosis of a patient. All components of the score are easily identifiable by clinicians.

Importantly, it turned out that PAD is not a simple high-risk condition, but displays a graded relationship between the above-mentioned three clinical dimensions and outcome. Indeed, the mortality risk among patients with PAD varies widely, with about a 4.5-fold increase in all-cause and cardiovascular mortality from the lowest to the highest score stratum. It is thus worthwhile to look more specifically to an individual`s disease state in order to predict the personal prognosis. Clearly, the discriminative power of the score including risk factors is no higher but rather lower than that of the PAD^{3D} alone. Our analysis was restricted to classical risk factors (diabetes, hypertension, smoking, dyslipidemia and gender) for outcome investigations, therefore we cannot exclude a potential prognostic impact of non-classical risk factors.

Furthermore, our findings call for more specific, customized interventions. For example, one could hypothesize that patients with a very high score in our model deserve a very intensive lowering of LDL cholesterol. Indeed, it has been shown by Bonaca *et al*. from the FOURIER trial that PAD patients have the highest absolute risk reduction by the PCSK-9 inhibitor Evolocumab and thus the lowest number-needed-to-treat (NNT).[27]

However, that study did not grade the cardiovascular risk of PAD in the way we propose here. Customized therapeutic interventions could further improve NNTs, improve cost-effectiveness, and ultimately stimulate specifically designed outcome trials. In this respect, it has been reported very recently from the ODYSSEY OUTCOMES trial, that the outcome of the PCSK9 inhibitor arm versus the control arm differs much more widely in patients with polyvascular than in those with monovascular or bivascular disease.[28]

There are several risk scores providing physicians with the opportunity to identify patients at risk and to treat them accordingly. In cardiology, at least two scores have come to great importance: the Thrombolysis In Myocardial Infarction (TIMI) risk score and the CHA_2DS_2VASC score.[10-12] Both scores have been well established and validated. They take risk factors (i.e. hypertension and diabetes), age, and cardiovascular manifestations of the disease into account. The CHA_2DS_2VASC score is more similar to our score than the TIMI score, since it avoids the use of either laboratory or technical examination results (i.e. ECG criteria in the TIMI score). By these scores, one can readily estimate the patient's risk of death and cardiac events (TIMI) or embolism/ stroke (CHA_2DS_2VASC).

Less well known than the TIMI risk or CHA_2DS_2VASC scores is the COPART risk score,[29-31] which aims to predict long–term mortality in PAD patients similarly to our proposed score. At present, it is the only risk score for PAD. In contrast to our proposed score, the COPART risk score uses mainly biochemical parameters (i.e. CRP, eGFR), presence/ absence of guideline recommended medication (i.e. antiplatelet drugs, statins, RAS inhibitors) and ABI levels. It also weights age stronger than in the other scores mentioned. Thus, at present we have two different approaches to a PAD risk score: COPART using

risk factors (classical and non-classical) and our PAD^{3D} score based on individual atherosclerosis stage.

In analogy to such scores, we included risk factors in a second step of an enlarged score, both, in the test cohort and in the validation cohort. In contrast to our primary PAD^{3D} score, the additive use of risk factors did not improve but rather deteriorated the predictive power. How can one explain this finding?

The value of risk factors, e.g. hypertension is to distinguish in clinically healthy subjects between those who are prone to develop ASCVD and those who are not. In patients with already established ASCVD, risk factors become less discriminative. As an example, the vast majority of our patients (85.3%) display hypertension. Thus, hypertension is no further a useful discriminant for risk prediction. Furthermore, risk factors undergo treatment in these patients and therefore their potential prognostic power must decrease considerably. In contrast, our proposed score is simple to evaluate, takes the stage of the atherosclerotic disease into account, and is not amenable to therapy.

One could argue that our proposed risk score does not consider the ABI in a population of PAD patients. Truly, the ABI levels have been shown to predict cardiovascular mortality and event rate,[19] as does the severity of symptoms.[18] However, one has to keep in mind that measurement of the ABI itself contains great inconsistencies, both due to prior lower limb revascularization, as well as due to observer variability. Intra- and inter-observer variability might range up to 10%.[32] Furthermore, in a population with diabetic patients (approximately 30% in PAD populations), ABI measurements are not reliable, due to increased arterial stiffness (mediasclerosis) leading to vessel incompressibility. Thus, falsely “normal” or even very high ABI levels may be recorded, and very high ABI levels

(≥1.4) are also associated with an increased mortality and morbidity in the manner of a U-shaped curve.[33] The Rutherford classification itself takes symptoms and ankle pressure into account. Thus, in an attempt to minimize the bias of the ABI measurement and variability, we decided against the inclusion of the ABI *per se* in our score.

Strengths and limitations.

The score proposed by us is simple to apply, since it assembles information that one can easily obtain from the patient`s history, i.e. (i) age, (ii) symptoms and from a short clinical examination including absolute ankle pressure measurement (Rutherford class), (iii) patients´ medical history regarding extent of atherosclerosis, i.e. additional coronary and cerebrovascular involvement. In contrast to other scores, there is no need for blood sampling. Thus, we believe the PAD^{3D} score will help to identify patients with extremely high cardiovascular risk readily within any symptomatic PAD population, also e.g. in a general practitioner setting. A further major strength of our study is that we report on both, a test as well as on a validation cohort, which underscores its validity.

As a limitation, the results of this study represent only a single-centre experience, however with a large PAD population. Furthermore, we have included only symptomatic PAD patients undergoing endovascular intervention. Asymptomatic PAD patients, as well as those being treated conservatively or undergoing surgical revascularisation did not enter our cohort. Therefore, the validity of our score for these entities remains to be established.

In conclusion, the central aim of our score is to better predict a patient's individual outcome based on his/her own clinical parameters. By taking age and clinical stage of the ASCVD disease into account, the PAD^{3D} score effectively predicts all-cause as well as

cardiovascular mortality in PAD patients on a very individual basis. There is no need to further add risk factors to the score. Our score is important to identify patients at high risk. The use of this score to guide interventions and more intense risk factor control is worth evaluation in clinical trials and in a broader population of PAD patients, e.g. those treated conservatively or surgically.

Conflict of interest

There is no conflict of interest or any relationships with industry.

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Table 1: Patient characteristics at baseline.

Demographics	**Patients**	**Test Cohort**	**Validation Cohort**
	n=1310	n=655	n=655
Age (years), mean ± SD	72.0 ± 11.7	71.6 ± 12.1	72.3 ± 11.2
Female gender, n [%]	472 [36.0]	232 [35.4]	240 [36.6]
family history of CV disease, n [%]	173 [13.2]	74 [11.3]	99 [15.1]
Current smoker, n [%]	809 [61.8]	390 [59.5]	419 [63.9]
Diabetes, n [%]	396 [30.2]	168 [25.6]	228 [34.8]
Hypertension, n [%]	1117 [85.3]	558 [85.2]	559 [85.3]
CAD, n [%]	557 [42.5]	263 [40.2]	294 [44.9]
CeVD, n [%]	209 [16.0]	96 [14.7]	113 [17.3]
Severity of PAD (Rutherford Class)			
Intermittent claudication			
1, n [%]	167 [12.7]	73 [11.1]	94 [14.4]
2, n [%]	438 [33.4]	193 [29.5]	245 [37.4]
3, n [%]	152 [11.6]	73 [11.1]	79 [12.1]
Critical limb ischemia			
4, n [%]	170 [13.0]	74 [11.3]	96 [14.7]

5 & 6, n [%]	383 [29.2]	241 [36.8]	142 [21.7]

PAD = peripheral artery disease; CeVD = cerebrovascular disease; CAD = coronary artery disease; CV = cardiovascular;

Table 2:

a) Three dimensional Peripheral Artery Disease (PAD^{3D}) Score.

Age (years)	Points	Rutherford Class	Points	Atherosclerosis extent	Points
<65	0	1, 2	1	PAD	0
65-75	1	3	2	+ CeVD	1
>75	2	4	3	+ CAD	3
		5, 6	4	PV (+ CeVD + CAD)	6

b) with additional Risk Factor Score (PAD^{RF})

Gender	Points	Smoking	Points	Diabetes	Points
Male	1	Yes	1	Yes	2
Female	-1	No	0	No	0
Hypertension	**Points**	**Dyslipidemia**	**Points**		
Yes	1	Yes	1		
No	0	No	0		

PAD = peripheral artery disease; PAD^{3D} = peripheral artery disease 3-dimensional risk score; PAD^{RF} = classical PAD risk factors; CeVD = cerebrovascular disease; CAD = coronary artery disease; PV = polyvascular

a) Distribution of points for age (dimension 1), Rutherford stage (dimension 2) and atherosclerotic extent (dimension 3). A minimum of 1 point and a maximum of 12 points are possible to reach for the PAD^{3D} Score. PAD itself and age below 65 are given 0 points.

b) Distribution of points when classical risk factors, like diabetes mellitus, arterial hypertension, dyslipidemia, smoking as well as gender are added for PAD^{3D} score. A potential minimum of 0 point and a maximum of 17 points are possible to reach for the PAD^{RF} Score.

Figure legends

Figure 1. Combined effects of age, peripheral arterial disease (PAD) severity and atherosclerotic extent. Survival outcomes for (A) all-cause mortality and (B) cardiovascular mortality in patients graded along different PAD^{3D} scores, as well as for different PAD^{RF} scores (C and D) in the Validation cohort.

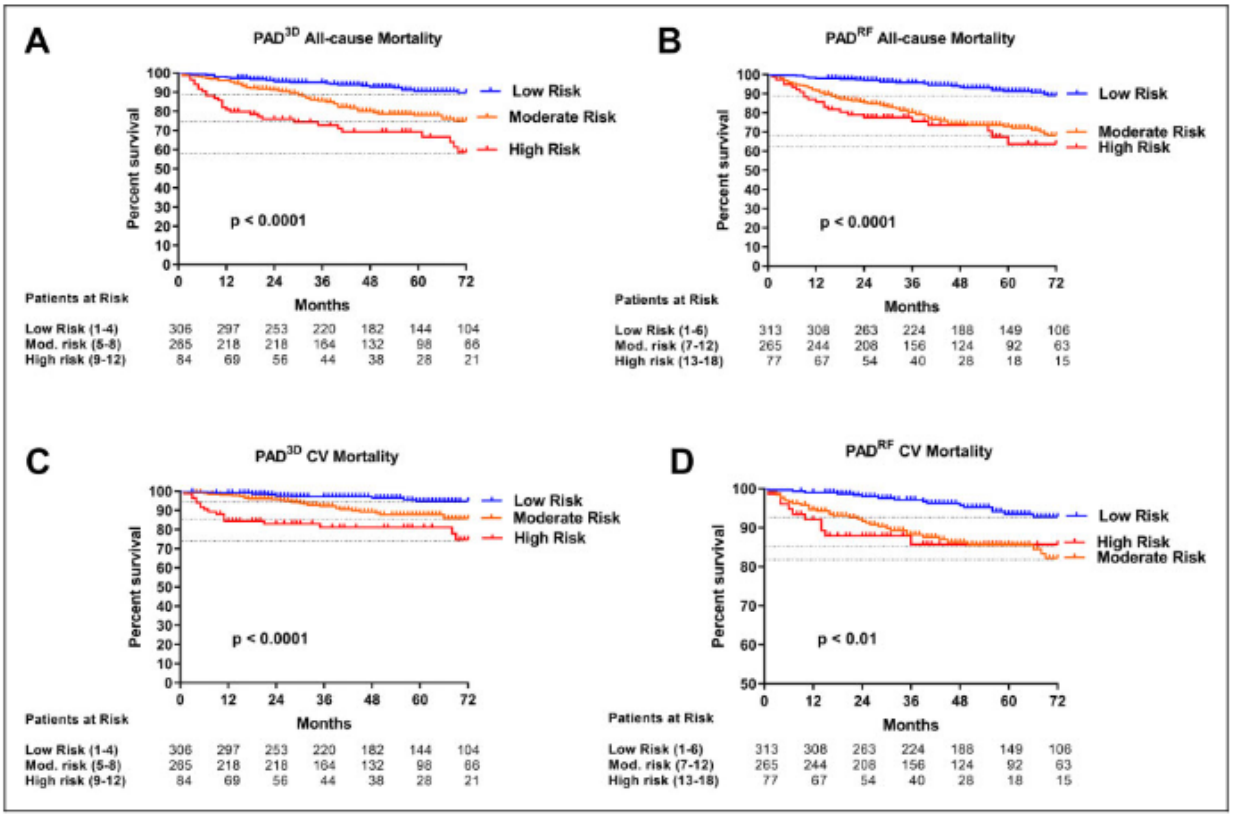


Figure 2. Peripheral arterial disease $(PAD)^{3D}$ score as prognostic predictor. Event rate of (A) all-cause mortality, (B) cardiovascular mortality for the PAD^{3D} score, as well as for the PAD^{RF} score (C and D) in the Validation cohort.

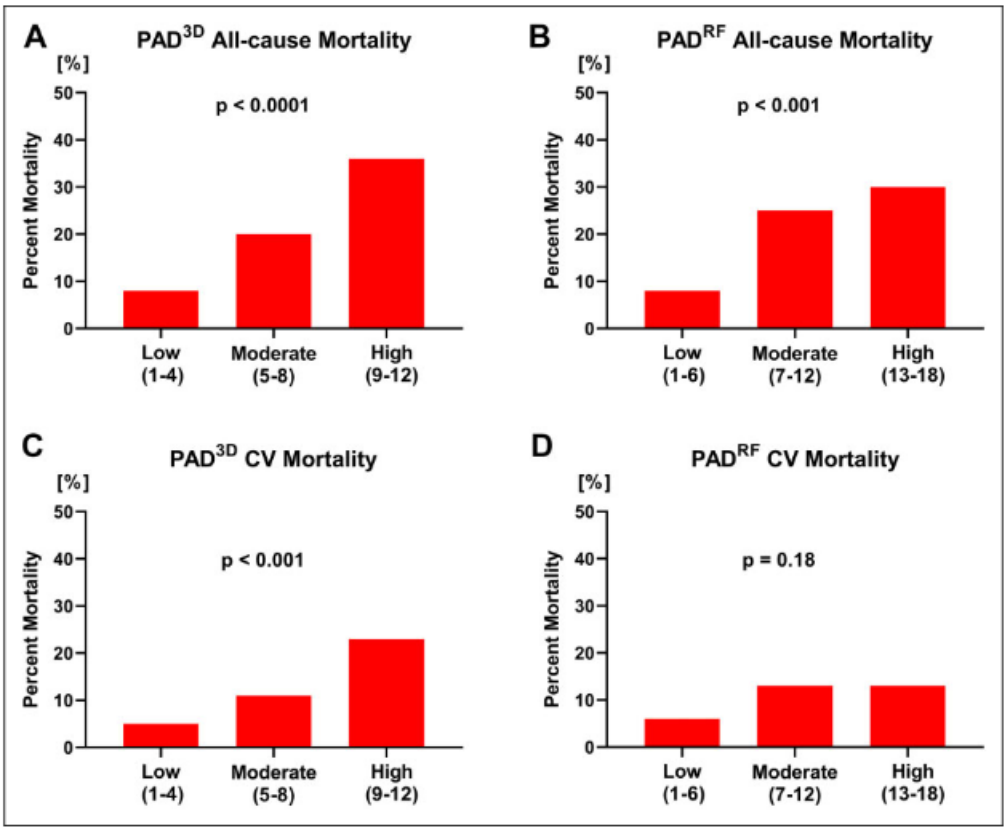
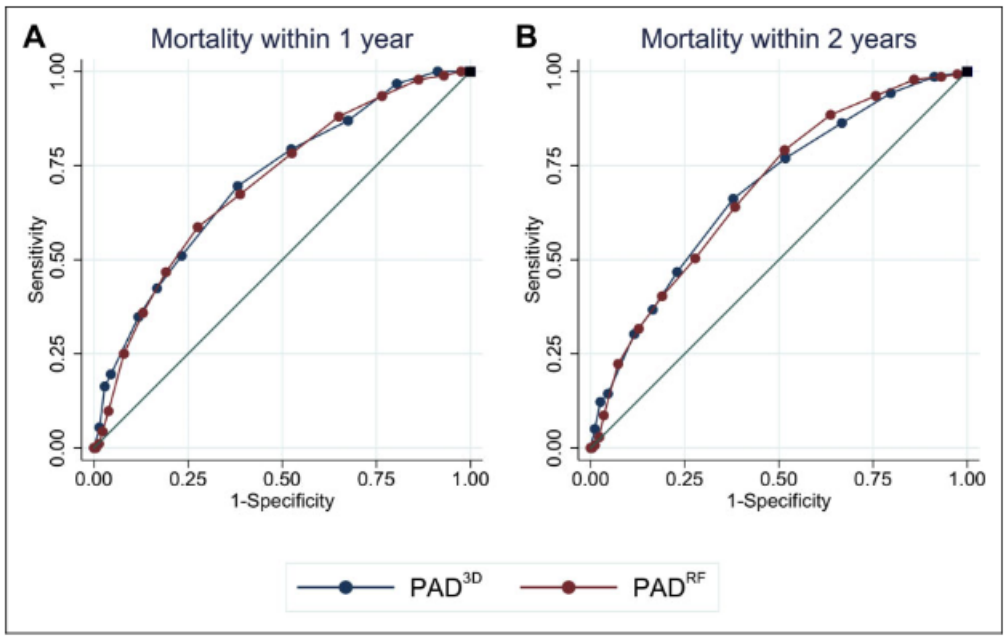


Figure 3. Area under receiver operating characteristic curves (AUROCs) between peripheral arterial disease (PAD)^{3D} and PAD^{RF}



No difference between both risk scores are seen either at (A) 1 year or (B) 2 year follow-up. The additional inclusion of classical risk factors did not increase discrimination for either score

Supplement

Suppl. Table 1: Causes of cardiovascular death.

n [%]	Cause of cardiovascular death total n = 91 [100]
cardiac	56 [62]
STEMI	9 [10]
NSTEMI	35 [38]
CABG	12 [13]
cerebrovascular	35 [38]
Stroke	25 [28]
Carotid operation	10 [11]

STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; CABG = coronary artery bypass graft surgery

Suppl. Table 2 a

Mortality within 1 month	PAD 3D Score	tp	tn	fn	fp	Sensitivity, %	Specificity, %	Post-test probability, %	Pre-test probability, %
									1%
	1	17	106	0	1187	100	8	1	
	2	17	241	0	1052	100	19	2	
	3	15	406	2	887	88	31	2	
	4	15	597	2	696	88	46	2	
	5	11	775	6	518	65	60	2	
	6	7	969	10	324	41	75	2	
	7	4	1054	13	239	24	82	2	
	8	3	1120	14	173	18	87	2	
	9	2	1222	15	71	12	95	3	
	10	2	1245	15	48	12	96	4	
	≥11	1	1271	16	22	6	98	4	
Mortality within 6 months									4%
	1	56	106	0	1148	100	8	5	
	2	55	240	1	1014	98	19	5	
	3	48	400	8	854	86	32	5	
	4	44	587	12	667	79	47	6	
	5	39	764	17	490	70	61	7	
	6	29	952	27	302	52	76	9	
	7	23	1034	33	220	41	82	9	
	8	18	1096	38	158	32	87	10	
	9	9	1190	47	64	16	95	12	
	10	6	1210	50	44	11	96	12	
	≥11	3	1234	53	20	5	98	13	
Mortality within 1 year									7%
	1	92	106	0	1112	100	9	8	
	2	89	238	3	980	97	20	8	
	3	80	396	12	822	87	33	9	
	4	73	580	19	638	79	48	10	
	5	64	753	28	465	70	62	12	
	6	47	934	45	284	51	77	14	
	7	39	1014	53	204	42	83	16	
	8	32	1074	60	144	35	88	18	
	9	18	1163	74	55	20	95	25	
	10	15	1183	77	35	16	97	30	
	≥11	5	1200	87	18	5	99	22	
Mortality within 18 months									10%
	1	118	97	2	1035	98	9	10	
	2	114	224	6	908	95	20	11	
	3	103	376	17	756	86	33	11	
	4	94	549	26	583	78	48	13	
	5	81	707	39	425	68	62	15	
	6	58	873	62	259	48	77	18	
	7	45	945	75	187	38	83	19	
	8	38	1004	82	128	32	89	22	
	9	18	1081	102	51	15	95	25	

	10	15	1101	105	31	13	97	32
	≥11	5	1117	115	15	4	99	24
Mortality within 2 years								12%
	1	137	87	2	914	99	9	11
	2	131	203	8	798	94	20	12
	3	120	333	19	668	86	33	13
	4	107	483	32	518	77	48	15
	5	92	622	47	379	66	62	17
	6	65	771	74	230	47	77	19
	7	51	836	88	165	37	84	21
	8	42	885	97	116	30	88	24
	9	20	955	119	46	14	95	27
	10	17	975	122	26	12	97	36
	≥11	7	990	132	11	5	99	35
Mortality within 3 years								17%
	1	171	79	2	739	99	10	14
	2	162	177	11	641	94	22	15
	3	147	285	26	533	85	35	17
	4	130	415	43	403	75	51	19
	5	111	524	62	294	64	64	21
	6	78	642	95	176	45	78	24
	7	60	694	113	124	35	85	26
	8	46	729	127	89	27	89	27
	9	22	782	151	36	13	96	31
	10	18	796	155	22	10	97	37
	≥11	7	808	166	10	4	99	33
Mortality within 4 years								23%
	1	199	70	2	605	99	10	17
	2	189	150	12	525	94	22	18
	3	170	244	31	431	85	36	19
	4	147	348	54	327	73	52	21
	5	124	438	77	237	62	65	24
	6	86	530	115	145	43	79	27
	7	66	577	135	98	33	85	29
	8	50	605	151	70	25	90	30
	9	24	645	177	30	12	96	33
	10	19	657	182	18	9	97	39
	≥11	8	667	193	8	4	99	38
Mortality within 5 years								30%
	1	213	53	2	456	99	10	18
	2	202	118	13	391	94	23	19
	3	178	187	37	322	83	37	20
	4	155	263	60	246	72	52	23
	5	130	327	85	182	60	64	25
	6	92	403	123	106	43	79	29
	7	71	439	144	70	33	86	32
	8	53	459	162	50	25	90	33

	9	26	487	189	22	12	96	35
	10	19	496	196	13	9	97	40
	≥11	8	504	207	5	4	99	43
Mortality within 6 years								39%
	1	226	40	2	317	99	11	19
	2	215	79	13	278	94	22	20
	3	189	129	39	228	83	36	21
	4	165	183	63	174	72	51	24
	5	138	232	90	125	61	65	27
	6	99	278	129	79	43	78	29
	7	77	308	151	49	34	86	34
	8	59	320	169	37	26	90	34
	9	27	340	201	17	12	95	34
	10	19	346	209	11	8	97	36
	≥11	8	353	220	4	4	99	40

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PAD RF Score	tp	tn	fn	fp	Sensitivity, %	Specificity, %	Post-test probability, %	Pre-test probability, %
Mortality within 1 month								1%
1	17	30	0	1263	100	2	1	
2	17	87	0	1206	100	7	1	
3	17	170	0	1123	100	13	1	
4	17	292	0	1001	100	23	2	
5	17	437	0	856	100	34	2	
6	16	597	1	696	94	46	2	
7	13	771	4	522	76	60	2	
8	8	911	9	382	47	70	2	
9	4	1021	13	272	24	79	1	
10	3	1104	14	189	18	85	2	
11	2	1175	15	118	12	91	2	
12	1	1238	16	55	6	96	2	
≥13	1	1262	16	31	6	98	3	
Mortality within 6 months								4%
1	56	30	0	1224	100	2	4	
2	55	86	1	1168	98	7	4	
3	54	168	2	1086	96	13	5	
4	52	288	4	966	93	23	5	
5	50	431	6	823	89	34	6	
6	45	587	11	667	80	47	6	
7	38	757	18	497	68	60	7	
8	31	895	25	359	55	71	8	
9	23	1001	33	253	41	80	8	
10	17	1079	39	175	30	86	9	
11	11	1145	45	109	20	91	9	
12	3	1201	53	53	5	96	5	
≥13	1	1223	55	31	2	98	3	
Mortality within 1 year								7%
1	92	30	0	1188	100	2	7	
2	91	86	1	1132	99	7	7	
3	90	168	2	1050	98	14	8	

	4	86	286	6	932	93	23	8
	5	81	426	11	792	88	35	9
	6	72	578	20	640	78	47	10
	7	62	745	30	473	67	61	12
	8	54	882	38	336	59	72	14
	9	43	985	49	233	47	81	16
	10	33	1059	59	159	36	87	17
	11	23	1121	69	97	25	92	19
	12	9	1171	83	47	10	96	16
	≥13	4	1190	88	28	4	98	13
Mortality within 18 months								10%
	1	119	27	1	1105	99	2	9
	2	118	78	2	1054	98	7	10
	3	117	157	3	975	98	14	10
	4	112	269	8	863	93	24	11
	5	106	405	14	727	88	36	12
	6	94	548	26	584	78	48	13
	7	76	699	44	433	63	62	14
	8	61	822	59	310	51	73	16
	9	50	921	70	211	42	81	18
	10	39	987	81	145	33	87	20
	11	28	1047	92	85	23	92	24
	12	11	1091	109	41	9	96	20
	≥13	4	1107	116	25	3	98	13
Mortality within 2 years								12%
	1	138	26	1	975	99	3	11
	2	137	69	2	932	99	7	11
	3	136	141	3	860	98	14	12
	4	130	243	9	758	94	24	13
	5	123	363	16	638	88	36	14
	6	110	485	29	516	79	48	15
	7	89	617	50	384	64	62	17
	8	70	723	69	278	50	72	18
	9	56	811	83	190	40	81	20
	10	44	873	95	128	32	87	23
	11	31	928	108	73	22	93	27
	12	12	966	127	35	9	97	23
	≥13	4	978	135	23	3	98	13
Mortality within 3 years								17%
	1	172	24	1	794	99	3	13
	2	171	64	2	754	99	8	14
	3	167	123	6	695	97	15	15
	4	161	214	12	604	93	26	16
	5	150	315	23	503	87	39	18
	6	134	409	39	409	77	50	19
	7	108	510	65	308	62	62	20
	8	84	598	89	220	49	73	22
	9	65	671	108	147	38	82	24
	10	51	720	122	98	29	88	27
	11	36	765	137	53	21	94	33
	12	13	790	160	28	8	97	25
	≥13	5	800	168	18	3	98	17
Mortality within 4 years								23%
	1	200	21	1	654	100	3	16
	2	199	57	2	618	99	8	16
	3	194	104	7	571	97	15	17
	4	187	182	14	493	93	27	19
	5	172	259	29	416	86	38	20

	6	153	343	48	332	76	51	22
	7	122	425	79	250	61	63	23
	8	92	495	109	180	46	73	24
	9	70	560	131	115	35	83	27
	10	54	597	147	78	27	88	30
	11	39	635	162	40	19	94	37
	12	15	656	186	19	7	97	32
	≥13	7	663	194	12	3	98	26
Mortality within 5 years								30%
	1	214	18	1	491	100	4	17
	2	212	48	3	461	99	9	18
	3	206	84	9	425	96	17	18
	4	197	143	18	366	92	28	20
	5	181	201	34	308	84	39	21
	6	161	261	54	248	75	51	23
	7	130	323	85	186	60	63	25
	8	98	376	117	133	46	74	26
	9	75	427	140	82	35	84	30
	10	57	451	158	58	27	89	31
	11	41	481	174	28	19	94	40
	12	16	497	199	12	7	98	38
	≥13	8	501	207	8	4	98	32
Mortality within 6 years								39%
	1	227	14	1	343	100	4	18
	2	225	31	3	326	99	9	19
	3	218	57	10	300	96	16	19
	4	208	98	20	259	91	27	21
	5	191	140	37	217	84	39	23
	6	170	186	58	171	75	52	25
	7	139	229	89	128	61	64	26
	8	107	266	121	91	47	75	28
	9	79	299	149	58	35	84	31
	10	61	314	167	43	27	88	32
	11	44	337	184	20	19	94	42
	12	17	349	211	8	7	98	41
	13	9	353	219	4	4	99	43

PAD = peripheral artery disease; PAD^{3D} = peripheral artery disease 3-dimensional risk score; PAD^{RF} = classical PAD risk factors;

Suppl. Table 2 b

			Area under ROC curve (95% CI)		
	N	Number of events	PAD^{3D}	PAD^{RF}	p
Mortality within 1 month	1310	17	0.669 (0.565 to 0.773)	0.697 (0.621 to 0.772)	0.628
Mortality within 6 months	1310	56	0.697 (0.629 to 0.764)	0.682 (0.617 to 0.748)	0.525
Mortality within 1 year	1310	92	0.708 (0.655 to 0.762)	0.702 (0.648 to 0.755)	0.680
Mortality within 18 months	1252	120	0.692 (0.643 to 0.741)	0.686 (0.639 to 0.734)	0.674
Mortality within 2 years	1140	139	0.684 (0.638 to 0.730)	0.686 (0.642 to 0.731)	0.876
Mortality within 3 years	991	173	0.683 (0.640 to 0.725)	0.683 (0.641 to 0.724)	0.998
Mortality within 4 years	876	201	0.677 (0.636 to 0.717)	0.676 (0.636 to 0.716)	0.953
Mortality within 5 years	724	215	0.674 (0.632 to 0.716)	0.676 (0.635 to 0.717)	0.878
Mortality within 6 years	585	228	0.673 (0.629 to 0.717)	0.678 (0.634 to 0.721)	0.702

AUROCs = Area under receiver operating characteristic curves; PAD = peripheral artery disease; PAD^{3D} = peripheral artery disease 3-dimensional risk score; PAD^{RF} = classical PAD risk factors;

Suppl. Figure 1. Age as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 2. Severity of the disease i.e. Rutherford stage as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 3. Extent of the disease as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 4. Gender as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 5. Hypertension as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 6. Diabetes mellitus as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 7. Smoking status as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 8. Dyslipidemia as a predictor of outcome. Kaplan-Meier curves of (A) all-cause mortality and (B) cardiovascular mortality over a 72-month-follow-up period in the Test cohort.

Suppl. Figure 9. Combined effects of age, PAD severity and atherosclerotic extent. Survival outcomes for (A) all-cause mortality and (B) cardiovascular mortality in patients graded along different PAD^{3D} scores, as well as for different PAD^{RF} scores (C and D) in the Test cohort.

PAD = peripheral artery disease; PAD^{3D} = peripheral artery disease 3-dimensional risk score; PAD^{RF} = classical PAD risk factors;

Suppl. Figure 10.

AUROC between PAD^{3D} and PAD^{RF} at (A) 1 month, (B) 6 months, (C) 18 months, (D) 3 years, (E) 4 years, (F) 5 years and (G) 6 years.

AUROCs = Area under receiver operating characteristic curves; PAD = peripheral artery disease; PAD^{3D} = peripheral artery disease 3-dimensional risk score; PAD^{RF} = classical PAD risk factors;