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Editor's Choice – The GermanVasc Score: A Pragmatic Risk Score Predicts Five Year Amputation Free Survival in Patients with Peripheral Arterial Occlusive Disease

Thea Kreutzburg [a], Frederik Peters [a], Jenny Kuchenbecker [a], Ursula Marschall [b], Regent Lee [c], Levente Kriston [d], E. Sebastian Debus [a], Christian-Alexander Behrendt [a,*]

[a] Department of Vascular Medicine, Research Group GermanVasc, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
[b] BARMER, Wuppertal, Germany
[c] Nuffield Department of Surgical Sciences, University of Oxford, Headington, UK
[d] Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

WHAT THIS PAPER ADDS

The first prediction score has been developed using machine learning techniques for long term outcomes in patients with a symptomatic peripheral arterial occlusive disease. The model exhibited high accuracy and adequate discrimination. The five year risk of amputation or death varied between 9% and 48% in patients with intermittent claudication, and between 25% and 88% in patients with chronic limb threatening ischaemia. In the routine clinical setting, the pragmatic score presented can help identify patients in need of intensified medical care and support decision making on invasive revascularisation opportunities.

Objective: Patients with peripheral arterial occlusive disease (PAOD) face an increased risk of both lower limb amputation and death. To date, it has been challenging to predict the long term outcomes for PAOD. The aim was to develop a risk score to predict worse five year amputation free survival (AFS).

Methods: In this retrospective analysis of claims data, symptomatic PAOD patients were split into training and validation sets. Variables in the model were patient age and sex, Elixhauser comorbidities, and the 190 most common secondary diagnoses. Penalised Cox regression (least absolute shrinkage and selection operator [LASSO]) with tenfold cross validation for variable selection was performed and patients were categorised into five risk groups using the ten most important variables. All analyses were stratified by intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI).

Results: In total, 87 293 patients with PAOD (female 45.3%, mean age 71.4 $\pm$ 11.1 years) were included in the analysis. The most important variable predicting worse five year AFS was patient age >80 years. The GermanVasc score exhibited good predictive accuracy both for IC (c statistic = 0.70, 95% confidence interval [CI] 0.69–0.71) and CLTI (c statistic = 0.69, 95% CI 0.68–0.70) with adequate calibration due largely to alignment of observed and expected risk. Depending on the cumulative point score, the five year risk of amputation or death ranged from 9% (low risk) to 48% (high risk) for IC, and from 25% to 88% for CLTI.

Conclusion: The GermanVasc score predicts worse five year AFS stratified for inpatients suffering from IC and CLTI, with good predictive accuracy. By separating low from high risk patients, the GermanVasc score may support patient centred consent.

Keywords: Chronic limb threatening ischaemia, Elastic net, Elixhauser comorbidity groups, Intermittent claudication, LASSO, Peripheral arterial occlusive disease

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INTRODUCTION

Patient centred health care should respect patients' individual needs without incurring delays. High quality medical evidence develops through research over decades, primarily by performing randomised clinical trials. Yet, in peripheral vascular medicine, trial data are frequently not available and therefore many guidelines are limited to consensus recommendations with a low level of evidence.[1–3]

* Corresponding author. Department of Vascular Medicine, Research Group GermanVasc, University Medical Centre Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany.
E-mail address: behrendt@hamburg.de (Christian-Alexander Behrendt).
Twitter: VASCevidence

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For patients with peripheral arterial occlusive disease (PAOD), quality of life is seriously impaired by the risk of amputation and death.[1] Knowledge about the individual probability of long term outcomes after hospitalisation for PAOD is sparse, therefore, it can be challenging to make the best choice from a wide range of possible invasive and best medical treatments.

Routinely collected data from registries or health insurance claims can help to quantify the risks for specific long term outcomes. With the FINNVASC registry study, a linear sum score for post-operative mortality and/or major lower limb amputation was developed. However, this score was developed for short term outcomes only.[4,5] Recruiting multicentre registry trials such as SWEDEPAD (Swedish Drug-elution Trial in Peripheral Arterial Disease),[6] BASIL-3 (BAlloon versus Stenting in severe Ischaemia of the Leg-3),[7] BEST-CLI (Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia),[8] and the GermanVasc registry trial[9] are currently collecting primary research data, including a follow up beyond 30 days. While those clinical registries usually need a certain time to collect enough data for valid prediction models, health insurance claims provide a large sample size suitable to use for data driven methods and predictive modelling. Although machine learning approaches have been used frequently in stroke and cardiac risk prediction, its use remains extremely rare in patients with PAOD.[10,11]

This study aimed to develop an easy to use score to estimate the five year probability of amputation free survival (AFS) of patients with PAOD, based on routinely collected health insurance claims data in Germany.

MATERIALS AND METHODS

Data source

Health insurance claims data from Germany's second largest insurance fund, BARMER, cover approximately nine million German citizens (10.8% of Germany's population). The German Modification of the World Health Organization's International Classification of Diseases 10th Revision (ICD-10-GM), Operations and Procedures Codes, and the German version of the international Anatomical Therapeutic Chemical classification for pharmacological treatment codes were used.

Study population

Adult patients aged 40 years and above treated in legally endorsed German hospitals and presenting with a primary diagnosis of symptomatic PAOD (stages II to IV, according to the Fontaine classification) from 1 January 2008 to 31 December 2016 were included. To identify an incident diagnosis of PAOD, a three year lookback was used (i.e., a disease free interval of three years). Patients with prior major amputation or death within 30 days after discharge were excluded (see Fig. 1).

Variables

Variables included age, sex (male *vs.* female), smoking, 30 different Elixhauser comorbidity groups (three year lookback),[12,13] year of discharge, history of prior myocardial infarction (MI) or prior stroke, atrial fibrillation (AF), dialysis, gangrene, discharge to rehabilitation or nursing home or

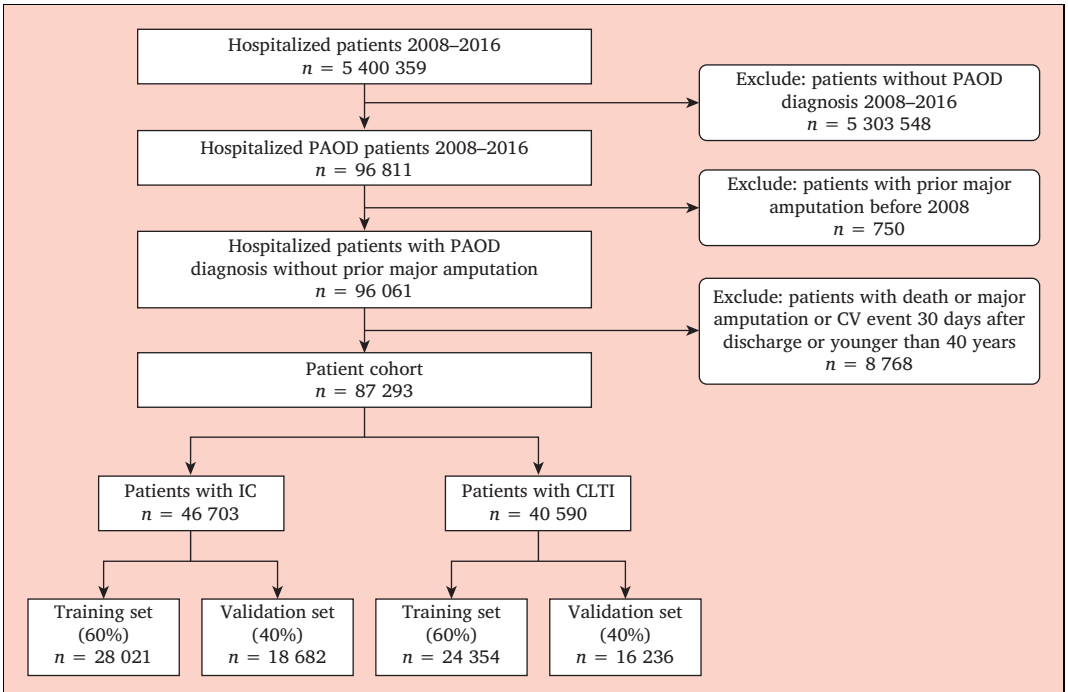

Figure 1. Flowchart for training and validation dataset of hospitalised patients with peripheral arterial occlusive disease (PAOD) stratified into intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI) groups. CV = cardiovascular event, including myocardial infarction or stroke.

hospice (three year lookback), and the 190 most common inpatient secondary diagnoses on admission. The patients were grouped according to age, to account for non-linear effects: 40—60 years; 61—70 years; 71—80 years; and ≥80 years. Missing data (0.5%) were deleted in a listwise manner (complete case analysis). All codes for the included variables are listed in Appendix S1 (see Supplementary Material).

Outcome

The primary outcome was death or major amputation above ankle level, measured as the composite endpoint of five year AFS after the index hospitalisation. Secondary outcomes were cardiovascular events, including MI or stroke after discharge.

Statistical analysis

To account for right censoring, a time to event framework using Cox proportional hazard models was used. The survival for five different risk groups from low to high risk was illustrated with Kaplan—Meier curves. The steps are outlined below. The implemented R code is given in the Appendix Table A5 (Supplementary Material), to encourage other research groups to use this risk score for better comparability.

Step 1: stratification. All analyses were stratified by Fontaine stages (according to the corresponding ICD-10 code) during the index stay: stage II for intermittent claudication (IC) *vs.* stage III/IV for chronic limb threatening ischaemia (CLTI).

Step 2: training and validation data set. The original dataset was separated into a training set (60%) and a validation set (40%). The predictive models and point score were developed in the training set, and model performance was assessed in the validation set.

Step 3: variable selection. Using the least absolute shrinkage and selection operator (LASSO) method, a parsimonious Cox survival model was estimated using a penalty term λ shrinking coefficients of irrelevant variables to zero (lambda).[14] The optimal λ was selected by tenfold cross validation. Using the non-zero variables only, the Cox survival model was re-estimated without a penalty term.

Step 4: top 10. To identify predictors contributing most to the generalisation power of the model from the previous step, variables were ranked based on the Breiman permutation method within the validation set.[15] The ten variables with c statistics (general term for area under the curve for a Cox regression; range 0—1) and highest Breiman importance were selected for use in the GermanVasc score.

Step 5: GermanVasc score. A final Cox model was fitted to the training set using only the 10 selected variables from step 4. The beta coefficients of this model were transformed to points (integer values), which, in sum, represent the GermanVasc score for individual risk prediction. The beta values were multiplied by ten and rounded to integers, following Austin *et al.*[16] This resulted in a pragmatic sum point score of the ten most important variables for usage in clinical routine care.

Step 6: model performance (discrimination). The discrimination of the variables was assessed in the validation set using the concordance statistics of c, a rank correlation coefficient accounting for censoring in the data. Further out of sample statistics were calculated for a subgroup of the validation set excluding high volume hospitals (>1000 interventions during the study period), a subgroup of the validation set excluding patients with an index stay after 2012, and cardiovascular event free survival as an outcome.

Step 7: model performance (calibration). Calibration of the prediction model was assessed by comparing the observed risk with the expected risk for each GermanVasc point value. The observed risk was measured by the Kaplan—Meier survival function fitted to the validation set and the expected risk by the Kaplan—Meier survival function fitted to the training set.

Step 8: risk groups. To categorise patients in five different risk groups, quantiles of the GermanVasc score points ($x_{0.2}$, $x_{0.4}$, $x_{0.6}$, and $x_{0.8}$) were used to find equal sized risk groups with low risk ($\leq x_{0.2}$) to high risk ($>x_{0.8}$). Risks for each group were estimated and plotted using Kaplan—Meier functions and hazard ratios (HRs) for each group using Cox regression models.

Step 9: summary sheet. To facilitate the application of the GermanVasc score, a summary sheet was created. Therein, points for each variable are displayed along with the risk associated with summarised points for each of the five risk groups. A tutorial and examples are provided in Fig. 2.

Sensitivity analyses

An elastic net approach was used as a sensitivity analysis (option alpha). The elastic net approach is known to perform better in feature selection if variables are highly correlated and more variables are used.[17] The results of these analyses are given in the Appendix (Supplementary Material).

Software

Data processing was performed with SAS version 9.04 (SAS Institute, Cary, NC, USA). Descriptive analyses, Cox models, LASSO, elastic net, model diagnostics, and illustrations were performed with R version 3.3 (*survival* and *glmnet* packages; R Foundation for Statistical Computing, Vienna, Austria). Visualisation was performed with Adobe Illustrator version 24.1.2 (Adobe, San Jose, CA, USA).

Reporting guidelines

Results were reported using the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[18]

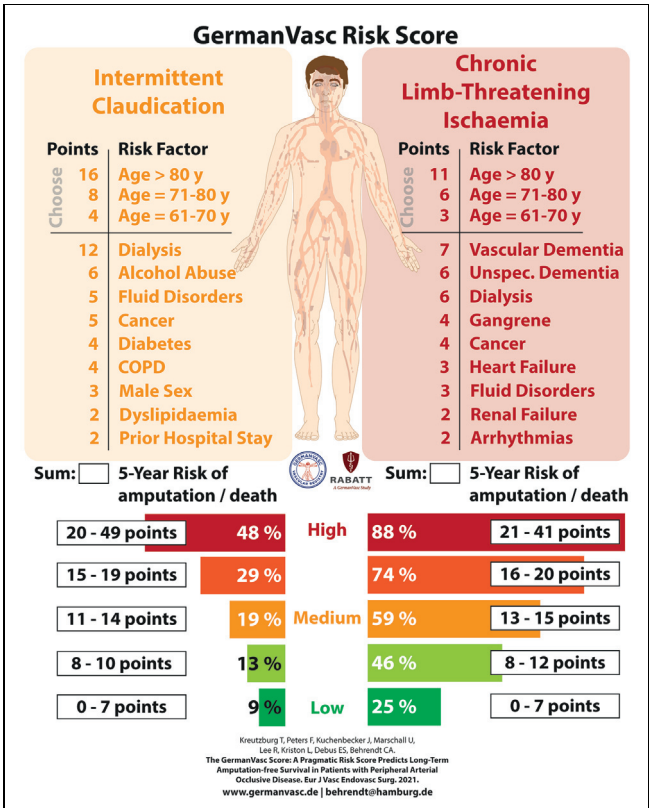

Figure 2. Summary sheet for the GermanVasc risk score stratified for intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI), including the five risk groups: low; low–moderate; moderate (medium); moderate–high; and high risk. The numbers before the risk factors are the point scores to be summarised for the presence of this risk factor. COPD = chronic obstructive pulmonary disease.

RESULTS

Baseline characteristics

In total, 87 293 patients with an incident symptomatic PAOD diagnosis between 2008 and 2016 (~10 000 per year; see Fig. 1) were included. Of these, 46 703 were diagnosed with IC (43% female) and 40 590 with CLTI (48% female). Patients with IC differed substantially from those with CLTI (Table 1). Patients with IC were younger (mean age 69 *vs.* 75 years); had fewer comorbidities such as congestive heart failure (14% *vs.* 33%), cardiac dysrhythmias (16% *vs.* 34%), or renal failure (19% *vs.* 37%); and were prescribed fewer medications (median 8 *vs.* 11). Within five years of index discharge, 19% of the patients with IC died and 1% had a major amputation, so that the composite endpoint was about 20%. For patients with CLTI, 50% died and 9% had a major amputation; the composite endpoint was 52%. The characteristics of the corresponding training and validation sets were largely similar (Table 1).

GermanVasc score

For the subgroup of patients with IC, the GermanVasc score exhibited good discrimination (model top 10 variables, c = 0.70, 95% confidence interval [CI] 0.69–0.71). The summarised point score ranged from 0 to 49. Patients with IC with lower point scores represented younger and healthier patients, and higher point scores older or sicker patients (Fig. A1a; see Supplementary Material). For the high risk group, the hazard ratio (HR) was 7.48 (95% CI 6.63–8.45), compared with the low risk group. The Kaplan–Meier survival curve (event rate for five year amputation or death in the low risk group was 8.7% and for the high risk group 47.6%) is given in Fig. 3(A). The 10 most important predictors of worse AFS were older age, male sex, cancer, absence of dyslipidaemia, alcohol abuse, chronic pulmonary disease, prior hospital stay, diabetes, dialysis, and fluid and electrolyte disorders (Tables 2 and 3). The point score also achieved good discrimination for the subgroups excluding high volume hospitals (c = 0.69, 95% CI 0.67–0.71 [Table A3; see Supplementary Material]) and excluding patients with an index stay after 2012 (c = 0.71, 95% CI 0.70–0.72) and for cardiovascular event free survival as the outcome (c = 0.63, 95% CI 0.62–0.64).

Likewise, for the subgroup of patients with CLTI, the GermanVasc score exhibited good discrimination (model top 10 variables, c = 0.69, 95% CI 0.68–0.70). The point score ranged from 0 to 41 (Tables 4 and 5), the distribution of the symmetric point score distribution is illustrated in Fig. A1b (Supplementary Material). For the high risk group, the HR was 7.83 (95% CI 7.24–8.48). The Kaplan–Meier survival curve (low risk event rate 25.2%; high risk five year rate of amputation or death 88.2%) is given in Fig. 3(B). The 10 most important predictors of worse AFS were older age, gangrene, unspecified dementia, dialysis, congestive heart failure, vascular dementia, cancer, fluid and electrolyte disorders, renal failure, and cardiac dysrhythmias (Tables 4 and 5). The point score also achieved good discrimination for the subgroups excluding high volume hospitals (c = 0.71, 95% CI 0.69–0.73 [Table A3; Supplementary Material]) and excluding patients with an index stay after 2012 (c = 0.70, 95% CI 0.69–0.71) and for cardiovascular event free survival as the outcome (c = 0.61, 95% CI 0.60–0.62).

Calibration

In the validation set, observed and expected risk showed a high degree of agreement for both IC and CLTI patients, except for high point score values, where only a few cases occurred. This is not only true for the full data, but also subgroups excluding high volume hospitals and excluding patients with index stay after 2012 (Fig. A2 – A4; Supplementary Material).

Sensitivity analysis

Elastic net. All analyses for five year AFS were performed with elastic net, which provided similar results for the top ten variables but with a slightly different ranking by Breiman's permutation method and the same range for the risk groups (from low risk to high risk). For the high risk IC group the HR was 7.18 (95% CI 6.35–8.11; c = 0.70 [95% CI 0.69–

Table 1. Patient characteristics of the training and validation dataset for patients with intermittent claudication (IC) and chronic limb-threatening ischaemia (CLTI)

	Total (n = 87 293)	IC training (n = 28 021)	IC validation (n = 18 682)	CLTI training (n = 24 354)	CLTI validation (n = 16 236)
Age − y	71.4 ± 11.1	68.8 ± 10.1	69.0 ± 10.2	74.5 ± 11.3	74.4 ± 11.3
Female sex	39 545 (45.3)	12 046 (43.0)	8 050 (43.1)	11 684 (48.0)	7 765 (47.8)
Elixhauser groups (3 y)					
Congestive heart failure	20 399 (23.4)	4 081 (14.6)	2 698 (14.4)	8 200 (33.7)	5 420 (33.4)
Cardiac dysrhythmias	21 351 (24.5)	4 530 (16.2)	3 081 (16.5)	8 205 (33.7)	5 535 (34.1)
Hypertension	68 384 (78.3)	21 437 (76.5)	14 316 (76.6)	19 587 (80.4)	13 044 (80.3)
Diabetes, complicated	24 004 (27.5)	4 116 (14.7)	2 792 (14.9)	10 268 (42.2)	6 828 (42.1)
Renal failure	23 728 (27.2)	5 045 (18.0)	3 533 (18.9)	9 074 (37.3)	6 076 (37.4)
COPD	12 634 (14.5)	3 655 (13.0)	2 507 (13.4)	3 915 (16.1)	2 557 (15.7)
Obesity	11 656 (13.4)	3 237 (11.6)	2 073 (11.1)	3 813 (15.7)	2 533 (15.6)
Smoking	15 330 (17.6)	5 919 (21.1)	3 880 (20.8)	3 385 (13.9)	2 146 (13.2)
Prior myocardial infarction	7 465 (8.6)	2 218 (7.9)	1 499 (8.0)	2 274 (9.3)	1 474 (9.1)
Prior stroke	7 307 (8.4)	1 545 (5.5)	1 031 (5.5)	2 846 (11.7)	1 885 (11.6)
Atrial fibrillation	12 801 (14.7)	2 379 (8.5)	1 580 (8.5)	5 303 (21.8)	3 539 (21.8)
Nursing care, discharge reason	2 076 (2.4)	119 (0.4)	86 (0.5)	1 141 (4.7)	730 (4.5)
Rehabilitation, discharge reason	5 367 (6.1)	1 147 (4.1)	761 (4.1)	2 109 (8.7)	1 350 (8.3)
Dialysis	1 812 (2.1)	180 (0.6)	122 (0.7)	880 (3.6)	630 (3.9)
Diagnosis (index stay)					
Dyslipidaemia, E78	28 580 (32.7)	10 812 (38.6)	7 111 (38.1)	6 399 (26.3)	4 258 (26.2)
Dementia, F03	1 711 (2.0)	107 (0.4)	73 (0.4)	918 (3.8)	613 (3.8)
Polypharmacy	9 (5–13)	8 (5–11)	8 (5–12)	11 (7–16)	11 (7–16)
Follow up time − d	1 503 (839–1825)	1 825 (1134–1825)	1 804 (1127–1825)	1 131 (481–1825)	1 144 (475–1825)
Antithrombotics	40 437 (46.3)	11 760 (42.0)	8 018 (42.9)	12 353 (50.7)	8 306 (51.2)
Lipid lowering drugs	39 431 (45.2)	14 271 (50.9)	9 546 (51.1)	9 280 (38.1)	6 334 (39.0)
Antihypertensive	72 602 (83.2)	22 557 (80.5)	15 041 (80.5)	20 971 (86.1)	14 033 (86.4)
Event rate within five years					
Composite endpoint: all cause death or major amputation	30 635 (35.1)	5 514 (19.7)	3 728 (20.0)	12 852 (52.8)	8 541 (52.6)
All cause death	29 129 (33.4)	5 323 (19.0)	3 592 (19.2)	12 118 (49.8)	8 096 (49.9)
Major amputation	4 256 (4.9)	401 (1.4)	255 (1.4)	2 169 (8.9)	1 431 (8.8)
Myocardial infarction	10 180 (11.7)	3 073 (11.0)	2 142 (11.5)	3007 (12.3)	1958 (12.1)
Stroke	11 874 (13.6)	3 541 (12.6)	2 295 (12.3)	3 596 (14.8)	2 442 (15.0)

Data are presented as n (%), mean ± standard deviation, or median (interquartile range). COPD = chronic obstructive pulmonary disorder.

0.71]), and for patients in the high risk CLTI group the HR was 7.83 (95% CI 7.24–8.48; c = 0.69 [95% CI 0.68–0.70]). The results are given in full in Tables A1 and A2 (Supplementary Material).

Summary sheet

All relevant information is provided in the summary sheet (Fig. A5; see Supplementary Material).

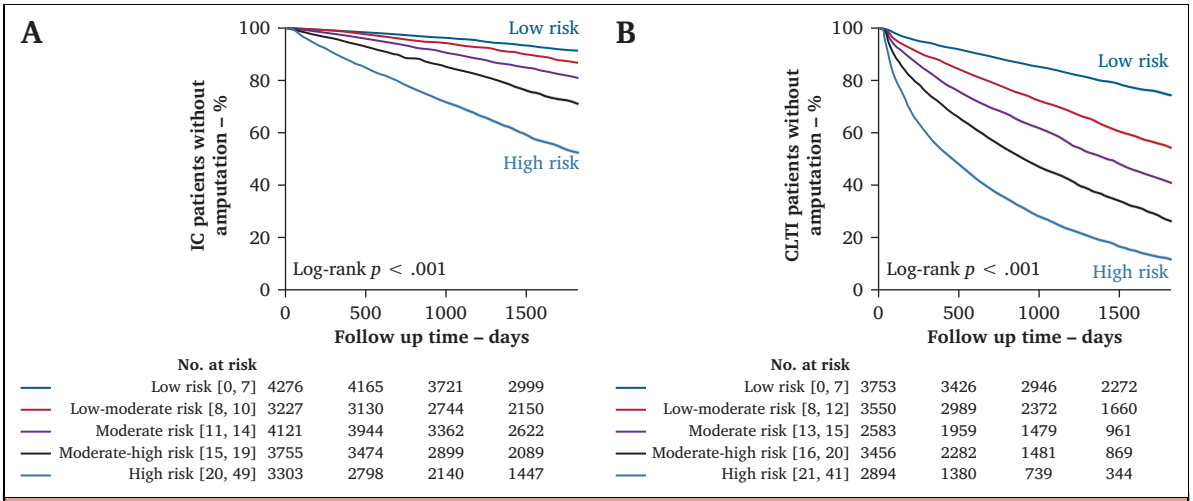

Figure 3. Cumulative Kaplan–Meier estimate of five year amputation free survival for GermanVasc score with the top 10 variables stratified for (A) intermittent claudication (IC) and (B) chronic limb threatening ischaemia (CLTI) for five risk groups: low; low–moderate; moderate; moderate–high; and high risk.

Table 2. Cox regression model prediction for five year amputation free survival for intermittent claudication in 46 703 patients: least absolute shrinkage and selection operator method with hazard ratios (HR) and 95% confidence intervals (CIs); the top 10 variables; and points for risk score based on highest Breiman importance

Variable	HR (95% CI)	Importance (Breiman)*	GermanVasc score
Age − y			
>80 (ref. 40–60)	4.80 (4.35–5.30)	1 168	16
71–80 (ref. 40–60)	2.21 (2.02–2.43)	552	8
61–70 (ref. 40–60)	1.50 (1.36–1.66)	144	4
Male sex	1.33 (1.26–1.41)	73	3
Cancer	1.62 (1.48–1.77)	69	5
Absence of dyslipidaemia (E78)	1.21 (1.14–1.27)	44	2
Alcohol abuse	1.75 (1.56–1.97)	33	6
Chronic obstructive pulmonary disease	1.56 (1.46–1.67)	31	4
Prior hospital stay	1.25 (1.18–1.32)	27	2
Diabetes	1.46 (1.38–1.55)	26	4
Dialysis	3.31 (2.74–3.98)	17	12
Fluid and electrolyte disorders	1.61 (1.51–1.71)	16	5

* Breiman importance multiplied by 10 000.

Table 3. Cox regression model prediction for five year amputation free survival for intermittent claudication in 46 703 patients: hazard ratios (HR) and 95% confidence intervals (CIs) and five year risk of amputation or death in five groups ranked from "low risk" to "high risk"

5 y risk of amputation or death*	HR (95% CI)	Amputation or death after 5 y − %	Range 0–49
Low risk	Reference	8.7	0–7
Low–moderate	1.54 (1.32–1.79)	13.0	8–10
Moderate	2.37 (2.07–2.70)	19.1	11–14
Moderate–high	3.82 (3.37–4.34)	28.9	15–19
High risk	7.48 (6.63–8.45)	47.6	20–49

* c = 0.70 (95% CI 0.69–0.71).

DISCUSSION

In this large scale health insurance claims data analysis, two pragmatic point scores were developed exhibiting high predictive accuracy and adequate discrimination between risk groups to predict worse five year AFS in patients with IC and CLTI. The scores were based on a data driven machine learning approach on longitudinal data. Owing to the advantages of the study sample, as compared with other data sources, there was only a small amount of missing data and no losses to follow up.[19]

Previous risk scores have been developed to predict outcomes in comparable target populations such as FINNVASC (3 925 patients with CLTI, 1991–1999, 30 day follow up),[4,5] the PREVENT-III risk score (1 166 patients with CLTI, 2003–2007, one year follow up),[20] the ERICVA simplified score (672 patients with CLTI, 2005–2010, one year follow up),[21] the

Table 4. Cox regression model prediction for five year amputation free survival for chronic limb threatening ischaemia in 40 590 patients: least absolute shrinkage and selection operator method with hazard ratios (HR) and 95% confidence intervals (CIs), the top 10 variables, and points for the risk score based on highest Breiman importance

Top 10 variables	HR (95% CI)	Importance (Breiman)*	GermanVasc score
Age − y			
>80 (ref. 40–60)	2.94 (2.72–3.17)	1 339	11
71–80 (ref. 40–60)	1.84 (1.70–1.99)	341	6
61–70 (ref. 40–60)	1.39 (1.28–1.51)	76	3
Gangrene	1.55 (1.48–1.62)	148	4
Unspecified dementia (F03)	1.87 (1.74–2.01)	46	6
Dialysis	1.74 (1.61–1.88)	41	6
Congestive heart failure	1.37 (1.32–1.43)	38	3
Vascular dementia (F01)	2.02 (1.84–2.21)	31	7
Cancer	1.47 (1.39–1.57)	31	4
Fluid and electrolyte disorders	1.34 (1.29–1.39)	29	3
Renal failure	1.26 (1.21–1.31)	20	2
Cardiac dysrhythmias	1.23 (1.18–1.28)	17	2

* Breiman importance multiplied by 10 000.

Table 5. Cox regression model prediction for five year amputation free survival for chronic limb threatening ischaemia in 40 590 patients: hazard ratios (HR) and 95% confidence intervals (CIs) and five year risk of amputation or death in five groups ranked from "low risk" to "high risk"

5 y risk of amputation or death*	HR (95% CI)	Amputation or death after 5 y − %	Range 0–41
Low risk	Reference	25.2	0–7
Low–moderate	2.06 (1.89–2.24)	45.5	8–12
Moderate	3.06 (2.81–3.33)	59.1	13–15
Moderate–high	4.61 (4.26–4.99)	73.7	16–20
High risk	7.83 (7.24–8.48)	88.2	21–41

*c = 0.69 (95% CI 0.68–0.70).

COPART (COhorte de Patients ARTériopathes) risk score (184 patients with IC, 2002–2004, five year follow up),[22] Arruda-Olsen *et al.* (1 676 patients with PAOD, 1998–2011, five year follow up),[23] or the SMART (Second Manifestations of Arterial Disease) risk score (5 788 patients with PAOD, 1996–2010, five year follow up).[24] and van Walraven *et al.*[25] who developed a comorbidity score using a large administrative database from Canada to predict in hospital mortality (345 795 patients, 1996–2008, in hospital follow up). Ambler *et al.*[26] used logistic regression methods to highlight the impact of frailty on outcomes (413 vascular surgery patients, one year follow up). On closer consideration, these previous risk scores were partially limited by several methodological issues. They either represented only a small subset of the entire target population (e.g., patients with CLTI or IC) with 184 to 5 788 patients or predicted short and mid term outcomes only, although most events occur in the longer term. The largest prediction model included a rather non-specific inpatient population, while the risk scores were most likely context specific. Furthermore, the variable selection was frequently subject to an investigator bias and therefore not objectifiable for external evaluation. For instance, the FINNVASC and PREVENT-III scores both relied on only four variables. The current study confirmed previous findings while adding an objectifiable variable selection using data driven approaches on a large disease specific sample.

A suitable risk score predicting long term outcomes may support the choice of optimal treatment and informed consent.[27] As an example, the American College of Cardiology and American Heart Association guidelines recommend initiation of statin treatment if the risk of stroke or MI exceeds 7.5%.[28] Those risk adjusted recommendations certainly demand an evidence based risk stratification. Another central advantage of the GermanVasc risk score may be a likely better comparability of studies using administrative data. With the increasing importance of real world data in health services research, harmonisation of methods appears crucial. By using the GermanVasc score, a single metric variable can be used to adjust multivariable models for major composite endpoints.

Interestingly, age was by far the most relevant predictor of long term outcomes for both IC and CLTI patients in the current study, while some prior studies deemed age to be less relevant for outcomes in PAOD.[4] Rather, the current study results are in line with the extensive literature on biomarkers predicting mortality, where even complex models rarely perform better than age alone.[29]

Besides age, only three comorbidities (dialysis, fluid and electrolyte disorders, and cancer) were equally included both in the IC and CLTI models. The notable differences between the models for IC and CLTI underscore the need for stratified risk estimation in fundamentally different groups. In line with this, guidelines separate PAOD patients with IC and CLTI,[1,2] and most risk scores had been developed for patients with CLTI only, for example, the PREVENT-III score.[20] Recent findings on interventions, treatment patterns, and outcomes also confirmed a stratified approach by disease severity.[30,31]

This is the era of large datasets and rapid development of "big data" methods in medicine, especially in clinical predictions. However, most of the cardiovascular disease prediction models lack external validation.[32] Differences between the included target populations, the contextual validity, and marked varieties between healthcare systems must be considered. A risk score validated for a heterogeneous cohort in a certain country needs to be validated before applying to another cohort in a different country.[33] To date, the available risk scores have not been validated for the German population, and there are reports that even among European populations outcomes in vascular medicine are significantly different.[34] Besides validation, the clinical relevance of the research question should be more focused than big datasets and be easy to achieve statistical significance.[35]

Limitations

Firstly, for most of the study variables, only inpatient data were used. There was a possibility that a small population were undergoing invasive revascularisation at outpatient facilities. Unlike the USA system, the German reimbursement system thus far motivates physicians to perform revascularisations as inpatients. The coding of health care in outpatient facilities differs from that in hospitals. Hence, very few publications are available to shed light on this aspect. Secondly, there is an ongoing discussion about the advantages and limitations of health insurance claims data. Some variables require a composite of codes to approximate to the relevant risk factor (e.g., smoking). No information about certain clinical parameters, for example, ankle brachial index, body mass index, cholesterol, or further laboratory tests, is available in routinely collected administrative data. Encouragingly, owing to regular external cross validation and harsh penalties for the submission of false claims, major comorbidities and endpoints

are known to be of high internal validity. This is especially true for observations that must be reported to different institutions and authorities such as major surgery, blood transfusion, or mortality. Lastly, as with many other models, the current score lacks independent external validation. Differences between the included target populations, the contextual validity, and marked variations between healthcare systems must be considered. Prospectively collected registry data, clinical parameters, and patient reported outcomes can be used to complement and extend the risk score. External validation of the GermanVasc score will be performed according to appropriate model approaches with a hierarchical structure (clustered data) and subgroup comparisons presented elsewhere.

Future directions

The GermanVasc score will be continuously updated with new claims data and registry data collected in the future. The most recent version and an online calculator are available at https://riskscore.germanvasc.de.

The GermanVasc score developed in the current analysis may help patients and their physicians to predict individual five year AFS to support patient centred consent and treatment decision making. Patients at high risk may benefit significantly from being directed to an intensified treatment in line with demand.

Conclusion

The GermanVasc score predicts worse five year AFS stratified for inpatients suffering from IC and CLTI with good predictive accuracy. By separating low from high risk patients, the GermanVasc score may support patient centred consent.

CONFLICTS OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.11.013.

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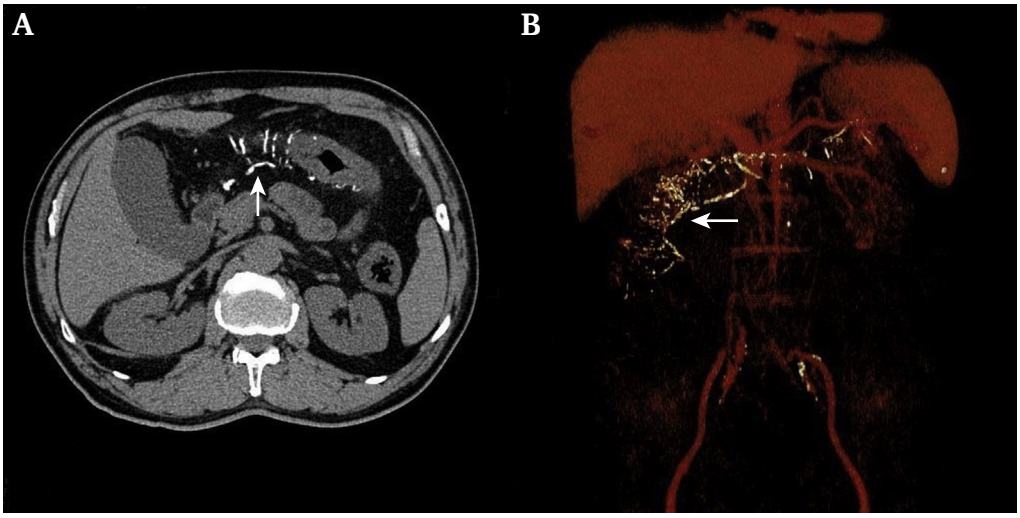
COUP D'OEIL

Phlebosclerotic Colitis

Hua Yi Zhang
Department of Vascular Surgery, Jiaxing Second Hospital, Jiaxing, Zhejiang, China



Phlebosclerotic colitis (PC) is a rare condition which impairs colonic venous return due to sclerosis and fibrosis of mesenteric veins, mostly observed in Asians. It may result in chronic ischemia, intestinal obstruction, and even perforation. A 64 year old male came complaining of abdominal pain and diarrhoea. He denied long term use of Chinese herbs. Physical examination showed diffuse tenderness without marked rebound tenderness. He underwent computed tomography angiography which revealed typical findings of PC: wall thickening and linear venous calcification of the ascending and transverse colon (A, B; arrows) Conservative treatment was initiated using alprostadil and low molecular weight heparin and his symptoms relieved remarkably.

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