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ORIGINAL ARTICLE

The Michigan Risk Score to predict peripherally inserted central catheter-associated thrombosis

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Essentials

- How best to quantify thrombosis risk with peripherally inserted central catheters (PICC) is unknown.
- Data from a registry were used to develop the Michigan Risk Score (MRS) for PICC thrombosis.
- Five risk factors were associated with PICC thrombosis and used to develop a risk score.
- MRS was predictive of the risk of PICC thrombosis and can be useful in clinical practice.

Summary. *Background:* Peripherally inserted central catheters (PICCs) are associated with upper extremity deep vein thrombosis (DVT). We developed a score to predict risk of PICC-related thrombosis. *Methods:* Using data from the Michigan Hospital Medicine Safety Consortium, image-confirmed upper-extremity DVT cases were identified. A logistic, mixed-effects model with hospital-specific random intercepts was used to identify factors associated with PICC-DVT. Points were assigned to each predictor, stratifying patients into four classes of risk. Internal validation was performed by bootstrapping with assessment of calibration and discrimination of the model. *Results:* Of 23 010 patients who received PICCs, 475 (2.1%) developed symptomatic PICC-DVT. Risk factors associated with PICC-DVT included: history of DVT; multi-lumen PICC; active cancer; presence of another CVC when the PICC was placed; and white blood cell count greater than 12 000. Four risk classes were created based on thrombosis risk. Thrombosis rates were 0.9% for class I, 1.6% for class II, 2.7% for class III and 4.7% for class IV, with marginal predicted probabilities of 0.9% (0.7, 1.2), 1.5% (1.2, 1.9), 2.6% (2.2, 3.0) and 4.5% (3.7, 5.4) for classes I, II, III, and IV, respectively. The risk classification rule was strongly associated with PICC-DVT, with odds ratios of 1.68 (95% CI, 1.19, 2.37), 2.90 (95% CI, 2.09, 4.01) and 5.20 (95% CI, 3.65, 7.42) for risk classes II, III and IV vs. risk class I, respectively. *Conclusion:* The Michigan PICC-DVT Risk Score offers a novel way to estimate risk of DVT associated with PICCs and can help inform appropriateness of PICC insertion.

Keywords: deep vein thrombosis; peripherally inserted central catheter; thrombosis; upper extremity; venous thromboembolism.

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Introduction

Although infrequent, approximately three-quarters of upper-extremity deep vein thromboses (DVTs) are associated with indwelling vascular catheters [1,2]. This association is not surprising; catheter insertion leads to endothelial damage, occupies the vein lumen (promoting venous stasis) and is often required in patients with hypercoagulability because of intercurrent illness or malignancy. Thus, placement of these devices satisfies Virchow's triad, leading to increased risk of venous thromboembolism (VTE).

Owing to ease of insertion and growing availability of vascular access teams, peripherally inserted central catheters (PICCs) are now among the most common type of central venous catheter inserted in hospitalized patients. Growing use of PICCs has led to the recognition that they are strongly associated with VTE [3–5]. In a meta-analysis of 62 studies (including 12 directly comparing patients who received PICCs with those who received conventional catheters), PICCs were associated with 2.5-fold greater

risk of DVT than traditional central venous catheters [6]. Notably, the magnitude of PICC-DVT was greater among patients with cancer and critical illness, populations that often receive PICCs for life-saving treatments [7,8]. Additionally, PICC-DVT is by no means rare in general medical patients; a single-site case-cohort study reported a 13-fold greater risk of thrombosis in patients who received PICCs across all medical sub-specialties [9].

Given the clinical significance of thrombosis associated with PICCs, a tool with which to classify DVT risk could be helpful in several ways. First, it could help identify patients at greater risk of this complication, and thus provide information on the risk of PICC use prior to placement. Second, a risk scoring tool may provide guidance for clinical testing, such as adopting a lower threshold for patients deemed high risk or those with few or vague symptoms. Finally, such a tool might also guide the duration and intensity of anticoagulation in patients who experience thrombosis, with consideration of extended courses for certain subgroups. In this study, we developed the Michigan Risk Score to estimate and calculate the risk of thrombosis related to PICCs in medical patients admitted to general wards or intensive care unit settings.

Methods

Study setting and participants

The study was conducted using data from the Michigan Hospital Medicine Safety (HMS) consortium, a 51-hospital collaborative quality initiative supported by Blue Cross Blue Shield of Michigan and the Blue Care Network. The design and setting of this consortium have been previously described [10–12]. In brief, HMS hospitals have been prospectively collecting data regarding PICC use and outcomes [3]. Adult patients admitted to a general medicine ward or intensive care unit (ICU) of a participating hospital who receive a PICC for any reason during clinical care are eligible for inclusion. Patients who are (i) under the age of 18, (ii) pregnant, (iii) admitted to a non-medical service (e.g. general surgery) or (iv) admitted under observation status are excluded.

At each hospital, dedicated, trained medical record abstractors use a standardized protocol to collect clinical data directly from health records of patients. Patients with PICCs are sampled on a 14-day cycle, and data from the first 17 cases that meet eligibility criteria within each cycle are collected. To ensure adequate representation of critically ill patients, seven of the 17 eligible cases include PICC placement in an ICU setting. All patients are followed until PICC removal, death or 70 days, whichever occurs first. To ensure completeness and accuracy of the data, staff from the University of Michigan perform annual on-site audits of all participating hospitals.

PICCs are defined as vascular access devices inserted into veins of the upper extremity that terminate at the cavoatrial junction; thus, midlines, central venous catheters or catheters placed in lower extremity veins are excluded. However, the presence of a central venous catheter (e.g. 'triple lumen catheter') in a limb or neck at the time of PICC insertion is captured. Data regarding PICC characteristics (e.g., gauge, lumens, tip position verification) and indication for PICC placement are obtained directly from vascular nursing or interventional radiology insertion notes or the physician's order for PICC placement. For this analysis, data from patients enrolled in the study between 2 January 2014 and 11 June 2016 were included.

Covariates

A detailed medical history, including comorbidities, physical findings and laboratory and medication data, was collected from the medical record. Standardized definitions using ICD-9 and Elixhauser criteria were used to define comorbidities at hospital admission [13]. Variables including age (< 64 vs. > 65 years), sex, race, body mass index, tobacco use (never, former, current), principal admitting diagnosis, history of upper or lower-extremity DVT (within 30 days, beyond 30 days, never), inpatient surgery within 30 days of PICC placement, chemotherapy or blood administration during hospitalization, trauma requiring hospitalization within 30 days, immobilizing plaster cast at the time of PICC placement, hip or knee replacement within 30 days of PICC placement, presence of active infection, existing central venous catheter when PICC was placed (yes/no), diabetes mellitus (uncomplicated vs. complicated by micro- or macrovascular complications), history of cerebrovascular accident or transient ischemic attack, history of myocardial infarction, sickle cell disease, venous thromboembolism prophylaxis (i.e. receipt of subcutaneous heparin on twice or thrice-daily regimens or use of enoxaparin at prophylactic doses), receipt of treatment-dose anticoagulation for any reason, aspirin, statin, erythropoiesis stimulating agents and antiplatelet medication administration, were also abstracted directly from the medical records. Active cancer was defined as admission for a cancer diagnosis or for chemotherapy. Serious lung disease was defined as receipt of invasive or non-invasive ventilatory support during hospitalization. Life-threatening illness was defined as any condition that required either ICU admission or transfer during hospitalization. Laboratory values including white blood cell (WBC) count (above or below 12 000 as this is the cut-off between abnormal and normal for most laboratories in the USA), hemoglobin, platelet count and international normalized ratio (INR) at the time of PICC placement were collected.

Ascertainment of outcomes

The primary outcome was radiographically confirmed upper-extremity DVT (defined as presence of a report in

the patient's medical record showing a compression or duplex ultrasound with visible thrombus, non-compressibility of the vein or computed tomography with similar positive findings) following PICC placement. At all sites, testing for DVT occurs only in the presence of clinical symptoms (e.g. arm pain and swelling). Patients with suspected DVT without confirmatory imaging findings or patients with documented pulmonary embolism but absence of a confirmed upper-extremity DVT were excluded.

Statistical analyses

Putative risk factors associated with PICC-related thrombosis were assessed according to a previously published [14] and validated conceptual model for PICC complications [15,16]. In accordance with this framework, covariates associated with PICC-DVT were first summarized as patient, provider and device factors using descriptive variables. Unadjusted associations of covariates with the probability of PICC-DVT were initially assessed with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The amount of missing data among the covariates considered was small (16 covariates contained some amount of missing data, with an average of 6% of values missing per variable). These missing data were imputed through a 10-fold multiple imputation procedure [17].

The Michigan Risk Score was developed in accordance with validated risk assessment tools [18–20], with validation of the final model performed using methodologic standards for prediction rules [21,22]. Both a Cox-proportional hazards model for time to PICC-DVT and a logistic mixed model were considered. As the predictive performance of the Cox model (as measured by the time-dependent ROC) was not superior to that of the logistic model and did not vary substantially over time, the simpler logistic model was chosen. Baseline covariates with an unadjusted P-value ≤ 0.10 in logistic mixed-effect models with hospital-specific random intercepts were considered as candidate predictors in a multivariable model. In keeping with recommended approaches [23], all candidate predictors were entered into the model, with the final multivariable model determined by a stepwise selection procedure based on covariate contributions to the model fit, as measured by the Schwarz criterion [24]. In order to obtain the most parsimonious model, covariates selected were examined in the mixed-effects model for their individual contribution to predictive performance, as determined by significance tests across competing model area under the curve (AUC) values [25].

Coefficients derived from the final model were assigned integer point values such that a total point score was calculated for each patient. The number of points assigned were based on the regression coefficient (rounding up to the closest whole integer) or what would be easiest for clinicians to recall (e.g. 2 points for double-lumen PICCs vs. 3 points for triple lumen devices) if the coefficients were similar. With respect to history of VTE, we divided this into categories: events within 30 days vs. events beyond 30 days. The rationale for this split relates to the facts that (i) the risk of VTE is greatest in the period most proximal to an event [26,27] and (ii) PICCs are often inappropriately removed and replaced in the setting of thrombosis typically within this 30-day window, potentially increasing risk of a recurrent event [3,28]. Based on this score, patients were assigned to risk class I, II, III or IV. The number of risk classes and the cut-off values for each class were selected so as to (i) maximize the AUC with respect to the classification rule and (ii) maintain increasing DVT rates in the empirical distribution with respect to each class.

The predictive performance of the model was assessed using several approaches. To assess calibration, a logistic mixed-effects model with risk class as a categorical predictor was used to determine the predicted VTE rate within each risk group. Marginal predicted event rates and discrimination were determined by integrating over the distribution of the random effects [29]. Additionally, a bootstrap internal validation procedure with 200 bootstrap resamples was performed to determine the calibration intercept, slope and estimated optimism of discrimination [30,31].

A two-sided P-value of less than 0.05 was used to indicate significance in all analyses. All analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.4.

Ethical and regulatory oversight

The University of Michigan Medical School's Institutional Review Board reviewed this study and it received a 'Not Regulated' status.

Results

Patient characteristics and outcomes

Of 23 010 patients who received PICCs, 475 (2.1%) developed symptomatic, image-confirmed PICC-DVT (Fig. 1). Of these 475 patients, 19 (4.0%) died during the follow-up period, whereas of the 22 535 patients without PICC-DVT, 1173 (5.2%) died during follow-up. Patients who developed PICC-DVT were similar to those who did not with respect to demographics such as age, gender and race. However, differences in comorbidities between the two groups on bivariate, unadjusted comparisons were noted. For example, patients with PICC-DVT more often had active cancer (11.6% vs. 6.1%, $P < 0.01$), history of cancer (28.0% vs. 23.4%, $P = 0.02$) and history of prior DVT (23.8% vs. 13.6%, $P < 0.01$). Patients with PICC-DVT also were more likely to receive their PICC in an

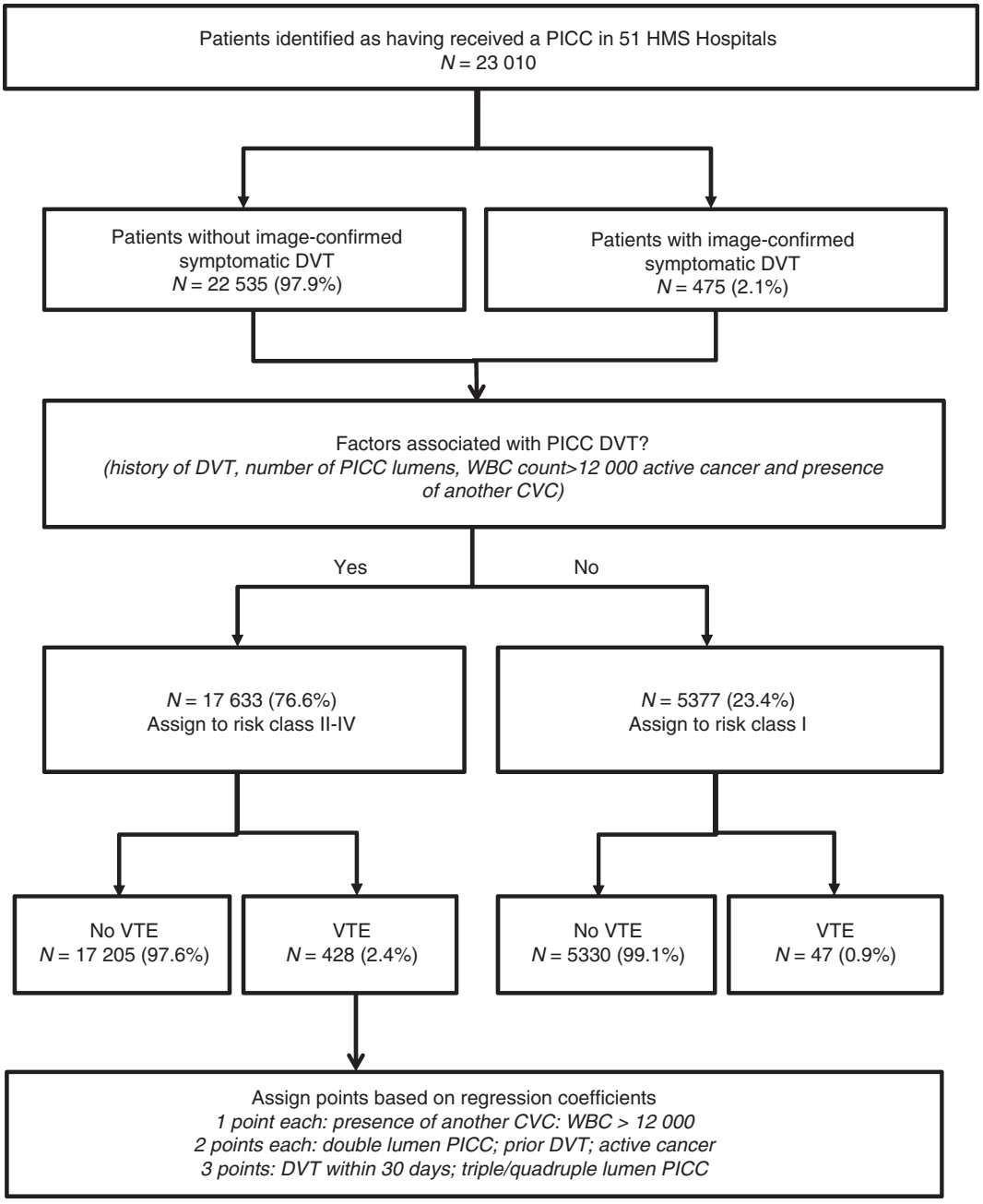

Fig. 1. Study flow diagram.

ICU setting compared with those without PICC-DVT (43.7% vs. 31.9%, $P < 0.01$). Accordingly, indications for PICC placement differed between groups. For example, patients with PICC-DVT more frequently had PICCs placed for chemotherapy (4.6% vs. 2.6%, $P < 0.01$) or difficult intravenous access (24.8% vs. 21.1%, $P = 0.05$) compared with those without.

With respect to device characteristics, no significant difference in the number of insertion attempts or arm of PICC insertion between those who did and those who did not develop PICC-DVT was observed. Notably, patients who received antimicrobial-coated PICCs experienced higher rates of thrombosis than those who received non-coated devices (12.8% vs. 6.9%, $P < 0.01$) (Table 1).

Associations between patient, provider and device characteristics and PICC-DVT are shown in Table 2, accounting for hospital-level clustering. Several patient characteristics, including active cancer and history of cancer (OR = 2.10 [95% CI = 1.57–2.82] and OR = 1.27 [95% CI = 1.04–1.56], respectively), history of DVT within 30 days of PICC placement (OR = 2.46 [95% CI = 1.69–3.57]), and critical illness (OR = 1.60 [95% CI = 1.33–1.94]) were significantly associated with

Table 1 General characteristics of patients with and without PICC-DVT (n = 23 010)

Category/variable	Modifier	No DVT (n = 22 535)	Confirmed DVT (n = 475)	P
Patient characteristics				
Male gender		11063 (49.1%)	242 (50.9%)	0.43
Race	White	16703 (76.0%)	335 (73.0%)	0.13
	Other	5269 (24.0%)	124 (27.0%)	
Age group	≥ 65 years	11088 (49.2%)	234 (49.3%)	0.98
	< 64 years	11447 (50.8%)	241 (50.7%)	
Body mass index (BMI)	Median (IQR)	28.76 (23.96–35.31)	27.58 (23.49–33.70)	0.02
Hyperlipidemia*		8308 (36.9%)	171 (36.0%)	0.70
Hypertension*		15416 (68.4%)	321 (67.6%)	0.70
Myocardial infarction†		937 (4.2%)	20 (4.2%)	0.95
Congestive heart failure†		3200 (14.2%)	53 (11.2%)	0.06
Peripheral vascular disorders*		3453 (15.3%)	57 (12.0%)	0.05
Cerebrovascular disease*		3414 (15.1%)	74 (15.6%)	0.80
Dementia*		1930 (8.6%)	38 (8.0%)	0.66
COPD†		2243 (10.0%)	46 (9.7%)	0.85
Rheumatoid arthritis†		238 (1.1%)	8 (1.7%)	0.19
Peptic ulcer disease*		856 (3.8%)	25 (5.3%)	0.10
Diabetes without complications*		4621 (20.5%)	88 (18.5%)	0.29
Diabetes with complications*		4430 (19.7%)	89 (18.7%)	0.62
Renal failure*		7834 (34.8%)	149 (31.4%)	0.12
Kidney transplant		131 (0.6%)	3 (0.6%)	0.89
Hemodialysis*		765 (3.4%)	24 (5.1%)	0.05
Peritoneal dialysis*		42 (0.2%)	0 (0.0%)	0.35
Hemi- or paraplegia†		1075 (4.8%)	27 (5.7%)	0.36
Mild liver disease*		1483 (6.6%)	24 (5.1%)	0.18
Moderate to severe liver disease*		863 (3.8%)	13 (2.7%)	0.22
Known HIV or AIDS*		161 (0.7%)	1 (0.2%)	0.19
History of cancer		5271 (23.4%)	133 (28.0%)	0.02
Active cancer		1376 (6.1%)	55 (11.6%)	< 0.01
Coagulopathy*		791 (3.5%)	27 (5.7%)	0.01
Charlson/Deyo comorbidity index	Median (IQR)	3 (1–5)	3 (1–5)	0.08
History of CLABSI		269 (1.2%)	8 (1.7%)	0.33
History of DVT	Within 30 days	643 (2.9%)	32 (6.7%)	< 0.01
	Prior history	2414 (10.7%)	81 (17.1%)	
History of PE	Within 30 days	348 (1.5%)	6 (1.3%)	< 0.01
	Positive history	1289 (5.7%)	42 (8.8%)	
History of any VTE Event	Within 30 days	874 (3.9%)	36 (7.6%)	< 0.01
	Positive history	2886 (12.8%)	94 (19.8%)	
Inflammatory bowel disease†		261 (1.2%)	13 (2.7%)	< 0.01
Serious lung disease†		6915 (30.7%)	189 (39.8%)	< 0.01
Life-threatening illness†		6990 (31.0%)	201 (42.3%)	< 0.01
Pneumonia†		4763 (21.1%)	116 (24.4%)	0.08
Sepsis†		7241 (32.1%)	161 (33.9%)	0.42
History of prior CVA/TIA		3843 (17.1%)	79 (16.6%)	0.81
Venous stasis*		1476 (6.5%)	22 (4.6%)	0.09
Smoking status	Current/former	13037 (57.9%)	276 (58.1%)	0.91
	Never	9498 (42.2%)	199 (41.9%)	
Statin		8034 (35.7%)	154 (32.4%)	0.15
Aspirin		7190 (31.9%)	118 (24.8%)	< 0.01
Other antiplatelet therapy		3068 (13.6%)	52 (10.9%)	0.09
White blood cell count*	Median (IQR)	9.20 (6.70–12.80)	10.40 (7.20–14.90)	< 0.01
Hemoglobin*	Median (IQR)	10.20 (8.80–11.70)	9.80 (8.60–11.50)	< 0.01
Platelet count*	Median (IQR)	226.00 (160.00–309.00)	228.50 (144.00–312.00)	0.37
International normalized ratio (INR)*	Median (IQR)	1.15 (1.02–1.39)	1.19 (1.08–1.34)	0.29
eGFR category*	< 15	610 (3.8%)	17 (5.1%)	0.39
	15–29	1295 (8.0%)	26 (7.8%)	
	30–44	1724 (10.6%)	26 (7.8%)	
	45–59	2170 (13.4%)	45 (13.5%)	
	≥ 60	10414 (64.2%)	219 (65.8%)	

Table 1 (Continued)

Category/variable	Modifier	No DVT (n = 22 535)	Confirmed DVT (n = 475)	P
Hospital LOS prior to PICC placement (days)	Median (IQR)	4 (2–7)	4 (2–8)	0.09
CVC or PICC in prior 6 months		4900 (21.7%)	138 (29.1%)	< 0.01
Presence of another CVC		3206 (14.2%)	109 (22.9%)	< 0.01
Provider characteristics				
Operator type	Vascular access nurse	15079 (66.9%)	286 (60.2%)	< 0.01
	Interventional radiologist	4535 (20.1%)	120 (25.3%)	
	Physician	237 (1.1%)	3 (0.6%)	
	Other			
Documented indication for PICC placement	Antibiotic therapy	8633 (38.3%)	137 (28.8%)	< 0.01
	Chemotherapy	580 (2.6%)	22 (4.6%)	< 0.01
	Difficult IV access	4763 (21.1%)	118 (24.8%)	0.05
	Medications requiring central venous access	2691 (11.9%)	52 (10.9%)	0.51
	Incompatible IV fluids/medication	345 (1.5%)	8 (1.7%)	0.79
	TPN	1171 (5.2%)	38 (8.0%)	< 0.01
	Unknown	7314 (32.5%)	159 (33.5%)	0.64
Location of PICC insertion	Outpatient	93 (0.4%)	0 (0.0%)	< 0.01
	Emergency room	385 (1.8%)	11 (2.5%)	
	ICU	6828 (31.9%)	194 (43.7%)	
	General floor	14114 (65.9%)	239 (53.8%)	
Placement attempts	> 1	2552 (11.5%)	47 (10.1%)	0.32
Arm selected for insertion	Right arm	15814 (70.2%)	327 (68.8%)	0.51
Vein selected for insertion	Basilic	13710 (60.8%)	275 (57.9%)	0.03
	Brachial	6912 (30.7%)	169 (35.6%)	
	Cephalic	1165 (5.2%)	14 (2.9%)	
	Other	748 (3.3%)	17 (3.6%)	
Device characteristics				
PICC dwell time (days)	Median (IQR)	12 (6–25)	12 (7–22)	0.44
PICC gauge	4 French	6729 (31.7%)	92 (20.0%)	< 0.01
	5 French	12691 (59.7%)	312 (68.0%)	
	≥ 6 French	1822 (8.9%)	55 (12.0%)	
Power PICC		20433 (90.7%)	422 (88.8%)	0.18
Antimicrobial coating		1556 (6.9%)	61 (12.8%)	< 0.01
Antithrombotic coating		385 (1.7%)	9 (1.9%)	0.76
Valved PICC		5589 (24.8%)	102 (21.5%)	0.10
Number of PICC lumens	Single	8481 (37.7%)	105 (22.1%)	< 0.01
	Double	10886 (48.4%)	277 (58.3%)	
	Triple/quad	3121 (13.9%)	93 (19.6%)	

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; CLABSI, central line-associated bloodstream infection; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; CVA, cerebrovascular accident; TIA, transient ischemic attack; eGFR, estimated glomerular filtration rate; LOS, length of stay; CVC, central venous catheter; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition; ICU, intensive care unit. Diabetes without complications = diabetes without documented retinopathy, nephropathy, neuropathy, cardio- or cerebrovascular events. *At time of PICC placement. †Within previous 30 days.

thrombosis. Thus, PICCs placed for chemotherapy (OR = 1.98 [95% CI = 1.27–3.10]), total parenteral nutrition (OR = 1.73 [95% CI = 1.23–2.44]) and difficult intravenous access (OR = 1.31 [95% CI = 1.05–1.64]) were also associated with thrombosis.

Multivariable models and risk score

Five factors emerged as being significantly associated with PICC-DVT: history of upper or lower-extremity DVT, number of PICC lumens, WBC count > 12 000, active cancer and presence of another CVC. Of the 23 010 patients, 23.4% (n = 5377) had none of these risk factors and were assigned to risk class I (i.e. lowest risk of thrombosis). The overall rate of PICC-DVT in this group was 0.9% (n = 47). In contrast, the remaining 76.6% (n = 17,633) of patients with one or more of the above factors experienced over a 2-fold increase in the incidence of PICC-DVT (2.4%, n = 428).

To create the Michigan Risk Score, we assigned points to each of the five factors based on their regression coefficients. Patients were assigned to one of four risk classes based on cumulative point totals (Table 3). Observed DVT rates were 0.9% for risk class I, 1.6% for class II, 2.9% for class III and 6.9% for class IV, with marginal predicted probabilities of 0.9% (0.7, 1.2), 1.5% (1.2, 1.9),

Table 2 Univariate associations between patient, provider and device factors and risk of PICC DVT (logistic mixed effect model)

Category/variable	Comparator/ referent group	Odds ratio (95% confidence interval)	*P*
Patient characteristics			
Male gender		1.10 (0.91, 1.32)	0.32
Race	White vs. Other	0.97 (0.77, 1.21)	0.76
Age group	≥ 65 vs. < 64	1.05 (0.88, 1.27)	0.57
Body mass index (BMI)	Per unit increase	0.99 (0.98, 1.00)	0.02
Hyperlipidemia	Yes vs. No	1.03 (0.84, 1.25)	0.80
Hypertension	Yes vs. No	0.99 (0.81, 1.20)	0.89
Myocardial infarction	Yes vs. No	1.04 (0.66, 1.65)	0.86
Congestive heart failure	Yes vs. No	0.71 (0.53, 0.96)	0.02
Peripheral vascular disorders	Yes vs. No	0.78 (0.59, 1.04)	0.09
Cerebrovascular disease	Yes vs. No	1.04 (0.81, 1.34)	0.76
Dementia	Yes vs. No	0.97 (0.69, 1.37)	0.88
COPD	Yes vs. No	0.95 (0.70, 1.30)	0.76
Rheumatoid arthritis	Yes vs. No	1.38 (0.67, 2.82)	0.38
Peptic ulcer disease	Yes vs. No	1.44 (0.95, 2.17)	0.09
Diabetes without complications	Yes vs. No	0.89 (0.70, 1.12)	0.32
Diabetes with complications	Yes vs. No	0.95 (0.75, 1.21)	0.69
Renal failure	Yes vs. No	0.89 (0.73, 1.09)	0.25
Kidney transplant	Yes vs. No	1.01 (0.32, 3.21)	0.98
Hemodialysis	Yes vs. No	1.32 (0.86, 2.01)	0.20
Hemi/paraplegia	Yes vs. No	1.23 (0.83, 1.82)	0.31
Mild liver disease	Yes vs. No	0.74 (0.49, 1.12)	0.15
Moderate/severe liver disease	Yes vs. No	0.66 (0.38, 1.15)	0.14
Known HIV/AIDS	Yes vs. No	0.29 (0.04, 2.05)	0.21
History of cancer	Yes vs. No	1.27 (1.04, 1.56)	0.02
Active cancer	Yes vs. No	2.10 (1.57, 2.82)	<0.01
Coagulopathy	Yes vs. No	1.45 (0.97, 2.18)	0.07
Charlson/Deyo comorbidity index	Per unit increase	0.97 (0.94, 1.01)	0.15
History of prior CLABSI	Yes vs. No	1.36 (0.67, 2.78)	0.39
History of prior DVT	Within 30 days vs. Never	2.46 (1.69, 3.57)	<0.01
	Positive history vs. Never	1.57 (1.13, 2.17)	
History of pulmonary embolism	Within previous 30 days vs. Never	0.84 (0.37, 1.89)	0.02
	Positive history vs. Never	1.57 (1.13, 2.17)	
History of any VTE event	Within previous 30 days vs. Never	2.11 (1.48, 3.00)	<0.01
	Positive history vs. Never	1.74 (1.38, 2.20)	
Inflammatory bowel disease	Yes vs. No	2.18 (1.24, 3.86)	<0.01
Serious lung disease	Yes vs. No	1.59 (1.31, 1.94)	<0.01
Life-threatening illness	Yes vs. No	1.60 (1.33, 1.94)	<0.01
Pneumonia	Yes vs. No	1.21 (0.98, 1.50)	0.08
Sepsis	Yes vs. No	1.15 (0.95, 1.41)	0.16
History of prior CVA/TIA	Yes vs. No	0.97 (0.76, 1.24)	0.79
Venous stasis	Yes vs. No	0.70 (0.46, 1.09)	0.11
Smoking status	Current/former vs. Never	1.01 (0.84, 1.22)	0.89
Statin	Yes vs. No	0.89 (0.73, 1.08)	0.23
Aspirin	Yes vs. No	0.73 (0.59, 0.90)	<0.01
Other antiplatelet therapy	Yes vs. No	0.77 (0.57, 1.03)	0.08
White blood cell count	Per unit increase	1.01 (1.00, 1.01)	<0.01
Hemoglobin	Per unit increase	0.96 (0.92, 1.00)	0.06
Platelet count	Per unit increase	1.00 (1.00, 1.00)	0.41
International normalized ratio	Per unit increase	1.00 (1.00, 1.00)	0.95
eGFR category	> = 60 vs. < 15	0.87 (0.48, 1.59)	0.63
	45–59 vs. < 15	0.71 (0.37, 1.39)	
	30–44 vs. < 15	0.97 (0.55, 1.73)	
	15–29 vs. < 15	0.98 (0.60, 1.60)	
Hospital LOS prior to PICC placement	Per unit increase	1.01 (1.00, 1.03)	0.05
CVC or PICC in prior 6 months	Yes vs. No	1.40 (1.14, 1.72)	<0.01
Existing CVC at time of PICC placement	Yes vs. No	1.74 (1.40, 2.17)	<0.01

Table 2 (Continued)

Category/variable	Comparator/ referent group	Odds ratio (95% confidence interval)	*P*
Provider characteristics			
Documented indication for PICC placement	Antibiotic therapy	0.73 (0.59, 0.91)	<0.01
	Chemotherapy	1.98 (1.27, 3.10)	<0.01
	Difficult IV access	1.31 (1.05, 1.64)	0.02
	Medications requiring central venous access	1.12 (0.82, 1.54)	0.47
	Incompatible IV fluids/medications	1.21 (0.59, 2.47)	0.61
	TPN	1.73 (1.23, 2.44)	<0.01
	Other/unknown	0.82 (0.67, 1.02)	0.07
Location of PICC insertion	ICU vs. General Medical Ward	1.68 (1.39, 2.03)	<0.01
	ER vs. General Medical Ward	1.69 (0.91, 3.1)	
Placement attempts	>1 vs. 1	0.92 (0.68, 1.26)	0.62
Arm selected for insertion	Right vs. Left	0.87 (0.71, 1.07)	0.18
Vein selected for insertion	Other vs. Basilic	1.15 (0.69, 1.91)	0.06
	Cephalic vs. Basilic	0.66 (0.38, 1.13)	
	Brachial vs. Basilic	1.23 (1.01, 1.51)	
Device characteristics			
PICC dwell time (days)	Per unit increase	1.00 (0.99, 1.00)	0.16
Gauge	Per unit increase	1.57 (1.33, 1.86)	<0.01
PICC length	Per unit increase	1.00 (0.98, 1.02)	0.87
Power PICC	Yes vs. No	0.88 (0.60, 1.29)	0.51
Antimicrobial coated	Yes vs. No	1.16 (0.82, 1.63)	0.40
Antithrombotic coated	Yes vs. No	0.84 (0.41, 1.71)	0.63
Valved PICC	Yes vs. No	0.86 (0.64, 1.17)	0.34
Number of PICC lumens	Triple/quad vs. Single	2.49 (1.84, 3.37)	<0.01
	Double vs. Single	1.88 (1.49, 2.38)	

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; CLABSI, central line-associated bloodstream infection; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; CVA, cerebrovascular accident; TIA, transient ischemic attack; eGFR, estimated glomerular filtration rate; LOS, length of stay; CVC, central venous catheter; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition; ICU, intensive care unit.

Table 3 Michigan Risk Score for PICC DVT (Stage 2 multivariable logistic mixed model)

Predictor variable	Status	Odds ratio (95% CI)	Points	*P*
Presence of another CVC when index PICC placed	Yes vs. No	1.43 (1.14, 1.79)	1	0.0022
WBC count at time of PICC insertion	> 12 vs. ≤ 12	1.46 (1.20, 1.77)	1	0.0001
Active cancer	Yes vs. No	1.97 (1.47, 2.65)	2	< 0.0001
Number of PICC lumens	Double vs. Single	1.63 (1.28, 2.07)	2	0.0025
	Triple/quad vs. Single	1.98 (1.45, 2.71)	3	
History of venous thromboembolism	Yes vs. Never	1.89 (1.47, 2.42)	2	< 0.0001
	Within 30 days vs. Never	2.19 (1.50, 3.18)	3	

CI, confidence interval; PICC, peripherally inserted central catheter; CVC, central venous catheter.

2.6% (2.2, 3.0) and 4.5% (3.7, 5.4) for classes I, II, III, and IV, respectively. In a logistic mixed-effects regression model with risk class as a categorical predictor, the risk classification rule was significantly associated with PICC-DVT ($P < 0.0001$), with odds ratios of 1.68 (95% CI, 1.19, 2.37), 2.90 (95% CI, 2.09, 4.01) and 5.20 (95% CI, 3.65, 7.42) for risk classes II, III and IV vs. risk class I, respectively (Table 4).

Internal validation of the Michigan Risk Score was performed using bootstrap resampling. The calibration intercept and slope were calculated to be −0.35 (95% CI, −0.78, 0.56) and 0.90 (95% CI, 0.78, 1.14), respectively. The areas under the receiver-operating-characteristics curve in the derivation data from the logistic mixed model and from the marginal predicted probabilities were 0.71 (estimated optimism of 0.04) and 0.65 (estimated optimism of 0.03), respectively.

The predictive performance of the model was unchanged by accounting for the ICU status of patients, with AUC values of 0.71 and 0.65 from the logistic mixed model and marginal predicted probabilities, respectively.

Discussion

Although increasingly used in clinical practice and safer to insert than traditional central venous catheters, accumulating evidence suggests that PICCs are associated with risk of thrombosis [5,6,9]. Despite growing recognition of

Table 4 Frequency and rate of PICC DVT by Michigan Risk Score class

Risk group/class (total points)	Observed events		Expected events	
	Patients (*N*)	VTE (*N*, %)	Risk of VTE OR (95% CI)	Probability of VTE % (95% CI)
Class I (0 points)	5377	47 (0.9%)	Referent	0.9% (0.7, 1.2)
Class II (1–2 points)	7808	122 (1.6%)	1.68 (1.19, 2.37)	1.5% (1.2, 1.9)
Class III (3–4 points)	7597	202 (2.7%)	2.90 (2.09, 4.01)	2.6% (2.2, 3.0)
Class IV (> 4 points)	2228	104 (4.7%)	5.20 (3.65, 7.42)	4.5% (3.7, 5.4)

VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval; PICC, peripherally inserted central catheter; CVC, central venous catheter.

this phenomenon, clinicians to date have had no way to identify patients who might be at untoward risk of DVT when considering PICC placement. To bridge this gap, we used data from medical records and contemporary modeling techniques to identify risk factors associated with PICC-DVT. These factors included: history of DVT, active cancer, the number of PICC lumens, white cell count > 12 000 at the time of PICC insertion and presence of another CVC. The Michigan Risk Score accurately distinguished those at low vs. high risk, with a 5-fold greater risk of thrombosis for those in the highest risk class compared with the lowest risk class. This scoring system is therefore a potentially useful tool that can provide information on the risk of thrombosis associated with PICCs and inform prevention efforts.

Some predictors of PICC-DVT identified in our study are similar to those reported by other investigators. For instance, Evans and colleagues reported that increasing catheter gauge (and resultant increase in lumens) was associated with thrombosis, such that efforts to decrease PICC diameter led to a reduction in DVT [32,33]. Similarly, the PADUA risk score (widely used to estimate risk of VTE in hospitalized patients) heavily weighs active cancer and history of thrombosis when estimating risk of thrombosis [34]. Our work builds on the work of these groups and further advances the field by: (i) focusing specifically on PICCs; (ii) distinguishing the contribution of increasing lumens with respect to risk of DVT; and (iii) distinguishing the greater importance of recent thrombosis (< 30 days) from a remote history. Additionally, we found that elevated white count during PICC insertion and presence of another central venous catheter when a PICC was placed were also predictive of thrombosis. Interestingly, most patients with another central venous catheter needing PICC placement anecdotally did so not for clinical reasons (e.g. need for greater vascular access), but rather as a transition strategy when leaving the ICU or to mitigate the risk of central line-associated bloodstream infection (CLABSI) with a device that has been inserted for 10 or more days. Changing central venous catheters has not been shown to reduce the risk of CLABSI in prior studies [35], and is not recommended by current guidelines [36]. Our data suggest, rather, that this practice and transitioning to PICCs is associated with increased risk of thrombosis. These findings have not been previously reported and have important clinical implications. For instance, avoiding PICC insertion in patients with another central venous catheter simply because they are leaving the ICU and/or deferring placement rather than considering an alternative device in patients with elevated WBC counts are clinically salient strategies that might reduce thrombosis and improve patient safety.

Our study has limitations. First, although we used several approaches to examine the performance of the Michigan Risk Score, external validation was not performed and is necessary before widespread use can be recommended. In relation to this, we used many covariates when fitting our model, which may have inadvertently led to model overfitting because we used a single dataset for derivation and validation. However, because we followed published and recommended approaches for developing the MRS [30,37], we believe the likelihood of this possibility is low. Second, the HMS consortium is focused purely on medical patients and samples from within a larger population. Although we include patients with cancer and those that are critically ill, lack of inclusion of other patient groups at high risk of thrombosis (e.g. surgical patients) and inclusion of a universal population may limit generalizability of the tool. Third, data used to develop this tool were collected through review of medical records and, as such, are susceptible to reporting bias.

Our study also has important strengths. First, we have created a novel risk tool with which to estimate the risk of PICC-DVT. Given the growing use of PICCs and paucity of risk models to examine the risk of thrombosis from these devices, the Michigan Risk Score represents an important contribution to the literature. Second, we expect that this tool will prove useful in helping to inform the decision as to whether use of a PICC is appropriate and safe for a given patient. With the introduction of appropriateness criteria to guide the use of PICCs [38], the Michigan Risk Score adds to a growing body of knowledge that helps improve decision making related to use of this device prior to insertion. Third, as has been

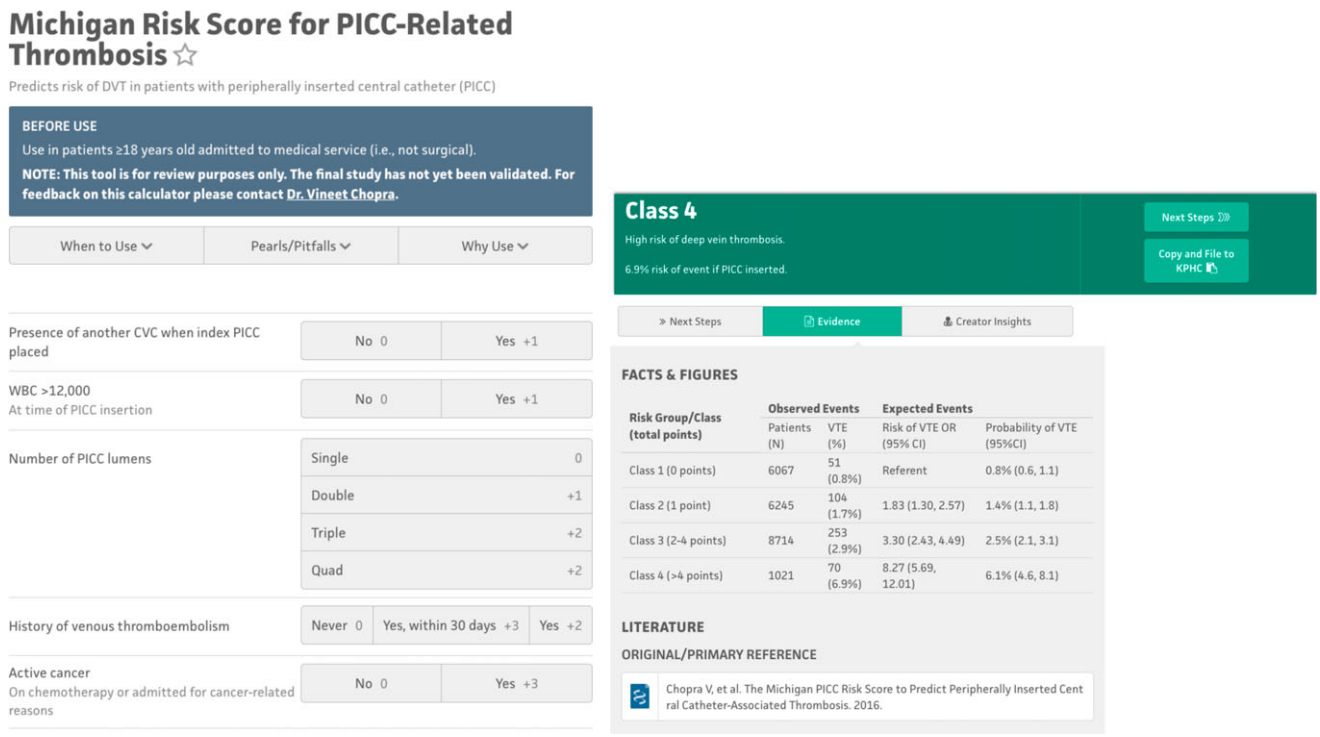

Fig. 2. Screenshots of risk calculator. Available online at https://web3dev.mdcalc.com/michigan-risk-score-picc-related-thrombosis [Color figure can be viewed at wileyonlinelibrary.com]

the case with other risk tools for venous thromboembolism [39–41], we expect that this score may prove useful in informing certain aspects of PICC care, such as the utility of diagnostic imaging when considering thrombosis (e.g. avoidance in low-risk patients) as well as the benefit of prolonged anticoagulation following confirmed thrombosis (extended use in high-risk categories). Although studies that test the usefulness of our tool for these issues are necessary, these are important clinical questions that the Michigan Risk Score may help answer. Finally, we have begun to explore methods to bring this tool to clinicians at the bedside. Given the proliferation of smartphones and apps, one approach is an online, web-based risk calculator that could facilitate point-of-care estimation of risk of thrombosis before placing a PICC. A demonstration version of this tool has been created and highlights how this model may prove extremely useful when making clinical decisions related to PICCs (Fig. 2).

In conclusion, we developed and internally validated the Michigan Risk Score to predict PICC-DVT. External validation of the score, followed by strategies to implement and evaluate the tool in clinical settings, would be welcomed.

Addendum

All authors were responsible for the conception and design. V. Chopra, A. Conlon, M. A. M. Rogers, S. Saint and S. Flanders were responsible for the analysis and interpretation. All authors drafted the manuscript and gave final approval of the manuscript.

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