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Derivation of a novel perioperative venous thromboembolism risk assessment model using National Surgical Quality Improvement Project data

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By

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M.D., Emory University School of Medicine, 2020

Advisor: Jordan A. Kempker, MD, MSc

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An abstract of

a thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

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Master of Science in Clinical Research

2024

Abstract

Derivation of a novel perioperative venous thromboembolism risk assessment model using National Surgical Quality Improvement Project data

By Eli Mlaver, MD

Venous thromboembolic events (VTE) remain a leading preventable cause of morbidity and mortality in postoperative patients despite nation-wide quality improvement efforts. Failure of consistent, standardized risk assessment contributes to these costly and devastating outcomes. Currently available risk assessment models (RAMs) are burdensome and lack procedural specificity or actionable thresholds for intervention; shortcomings which limit their utility within clinical workflows. The development of a parsimonious RAM designed for clinical workflows has the potential to increase adherence to risk assessment and prophylaxis administration, thereby improving the health outcomes of post-operative patients.

We applied multivariable logistic regression modelling with a clinically-guided forward selection process to the 2019 National Surgical Quality Improvement Project Public User File dataset in order to identify variables for inclusion in the new RAM. Procedural specificity was introduced by grouping Current Procedural Terminology (CPT) codes and creating a dichotomous variable capturing minimally invasive techniques. Integer point values were assigned to included variables to derive a VTE RAM. Model performance was compared to three currently available RAMs: the Caprini score, the COBRA model, and the American College of Surgeons (ACS) Risk Calculator.

Eleven variables were chosen for inclusion: age, BMI, functional status, American Society of Anesthesiologists Physical Status classification; history of steroid use, ascites, or cancer; pre-operative sepsis or blood transfusion; CPT group and minimally invasive surgery. The new FAST AS A CLOT model at a cutoff of 5 points has a lower c statistic (0.753) than the previously published c statistic for the ACS Risk Calculator (0.819), but has an 89% sensitivity for VTE outcomes in the NSQIP dataset as compared to 77% for COBRA and 62% for Caprini.

As it was derived with an emphasis on biological plausibility and face validity to clinicians, the FAST AS A CLOT model addresses many of the limitations of currently available RAMs. Validation within clinical workflows is still needed. If adopted, implementation within the electronic health may improve care quality and patient outcomes.

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Contents

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Abbreviations and Definitions

Arranged in alphabetical order.

ACS	American College of Surgeons
AHRQ	Agency for Healthcare Research and Quality
AUC	Area under the receiver operating curve
ASA-PS	American Society of Anesthesiologists Physical Status classification
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CDS	Clinical decision support
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPT	Current procedural terminology
CT	Computed tomography
DVT	Deep vein thrombosis
EHR	Electronic health record
NSQIP	National Surgical Quality Improvement Program
OR	Odds ratio
PATOS	Present at time of surgery
PE	Pulmonary embolus
PUF	Public User File
RAM	Risk assessment model
ROC	Receiver operating curve
RR	Relative rate
SIRS	Systemic inflammatory response syndrome
SSI	Surgical site infection
UTI	Urinary tract infection
VTE	Venous thromboembolism

1. Introduction

Venous thromboembolic events (VTE) remain a leading preventable cause of postoperative morbidity and mortality.[1] Surgery dramatically increases risk of VTE[2], and as a result, symptomatic VTE can occur in up to 25% of high-risk hospitalized surgical patients[3] and up to 60% of patients who undergo major surgery develop a DVT that is detectable by venography.[4] The public health impact of this problem is estimated as costing 300,000 lives[1] and $10B[5] annually in the United States from the combination of new VTE incidence and its myriad complications including recurrent VTE, chronic thrombo-embolic pulmonary hypertension, post-thrombotic syndrome, and chronic medication needs. Surgery accounts for approximately 24% of overall VTE incidence.[6] Due to the combination of stasis and vasodilation induced by anesthesia, endothelial injury caused by dissection, and indications for surgery which are often hypercoagulable states – all three elements of Virchow's triad – the operating room is a quintessential location for DVTs to form.

The risk of VTE is mitigated in large part by the administration of prophylactic anticoagulant medication starting prior to surgical incision[7], most commonly heparin or one of its derivatives. Other steps we can take to decrease thrombosis risk include pre-habilitation such as walking and smoking cessation, application of sequential compression devices on the patient's lower legs during and after surgery, and early post-operative mobility programs to decrease stasis. Unfortunately, despite two decades of quality improvement efforts, these chemical and mechanical prophylactic measures remain under-utilized.[1,8,9]

The challenge of translating evidence into practice is widely acknowledged.[10–12] Multiple studies have demonstrated inconsistent risk assessment and poor guideline adherence causing even high risk patients to not receive recommended prophylaxis the majority of the time.[10,13–15] In fact, internal review performed at Emory found that only 18% of surgical patients had received appropriate prophylaxis.[16] The ongoing prevalence of VTE has led the American College

of Surgeons to hold VTE as one of the foci of the National Surgical Quality Improvement Program (NSQIP). NSQIP recommends initiation of prophylaxis based on individualized risk stratification.[17] Standardization remains challenging due to patient heterogeneity, variation in risk assessment models (RAMs) and inconsistent prophylaxis patterns among providers including variation in timing, dosing, and duration of therapy.[3,13,18–20]

Furthermore, the use of prophylactic anticoagulation is not without theoretical risk. The fear of bleeding is cited as one of the top reasons for inconsistent prophylaxis. [3] Use of perioperative chemoprophylaxis is relatively contraindicated in some patients that are at high bleeding risk.[8,15] And studies have found that in select populations, such as those undergoing non-oncologic thyroid surgery[21], the risk and impact of bleeding may outweigh risk and impact of clotting. Thus, when focusing on VTE prophylaxis, bleeding outcomes are considered a balance measure, defined as a metric that must be tracked to ensure that there are not negative consequences to quality improvement efforts. In practice, surgeons must always balance the potential impact of these two conflicting morbidities, which likely contributes to the elusiveness of VTE as a quality improvement target.

The American Heart Association and International Society on Thrombosis and Haemostasis call on evidence-based tools to address ongoing gaps and improve care delivery.[22] The use of computerized clinical decision support (CDS) tools is a key strategy to standardize risk assessment and improve prophylaxis compliance.[23] There are multiple validated VTE risk assessment models (RAMs) that aim to serve this purpose, but each has limitations.

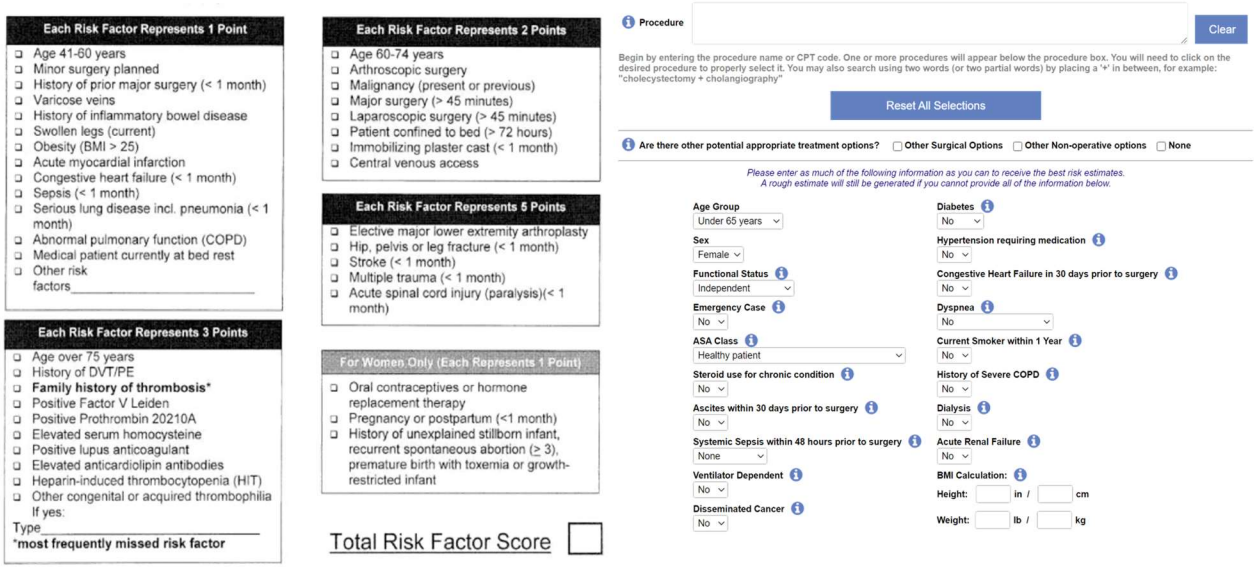


Figure 1 | Currently available VTE risk assessment models. Left: Caprini Score. Right: American College of Surgeons Risk Calculator

The most widely used VTE RAM in surgical practice is the Caprini Score (Figure 1, left).[24,25] However, the Caprini score can be cumbersome to calculate, requiring the identification of more than 30 clinical variables and manual score calculation that is estimated to take upwards of 6 minutes per patient.[26] This calculation is difficult to automate as the score requires elements of the patient's history that may not be consistently documented.[27] Surveys of 69 perioperative providers at our hospital reported that the time taken to estimate VTE risk using the Caprini model contributed to the low rate of model utilization and subsequent prophylaxis use,[16] agreeing with prior literature.[26] The long list of variables includes multiple labs that are not routinely measured. And after capturing so many variables, the score does not provide any procedural specificity beyond the extra points assigned to arthroplasties and orthopedic fixations. In other words, a given patient's Caprini risk assessment would be identical whether they are undergoing a laparoscopic cholecystectomy or an open colectomy. This limitation in particular has led many to attempt to validate the model with differing high-risk thresholds in different patient populations.[28] The variability of the risk categories defined by the model call into question its generalizability.[29]

Alternatively, the American College of Surgeons (ACS) provides VTE risk assessment as part of their online Risk Calculator (Figure 1, right).[30] This model uses 20 patient predictors in addition to the Current Procedural Terminology (CPT) code of the planned procedure to estimate risk. Capturing the CPT code does provide procedural specificity, a major strength of this model. There are, however, many limitations as well: First, the risk calculation is not transparent to providers or patients, and the algorithm cannot be automated into pre-operative workflows as it is proprietary. The Risk Calculator requires input of more than 20 variables, which is still quite cumbersome. Some of these variables are subjective or non-biological, such as whether the surgery is considered "emergent," which limits face validity of the model. Most importantly, there is also no specific projected risk rate defined as the threshold for chemoprophylaxis intervention, and validation studies have not defined actionable cut-offs.[20] This dramatically limits the utility of this RAM for CDS.

There is thus a need for an actionable risk assessment model that can be consistently used for CDS in perioperative workflows. Our prior work shows the promise of a simplified RAM. Our team developed a model called the COBRA score that captures just five variables: cancer, age, BMI, race, and the American Society of Anesthesiologists Physical Status (ASA-PS) classification[31]. This parsimonious model predicted risk of VTE with similar sensitivity as the Caprini model in a small pilot study.[18] In a larger institutional cohort of >10,000 patients, those with high COBRA scores had a relative risk for VTE outcomes of 2.7, suggesting that COBRA performs well and is clinically pertinent overall (Figure 2, left).[32] However, the model was found to perform better in some patient populations than others (Figure 2, right), highlighting the importance of procedural specificity for universal applicability. In addition, COBRA was

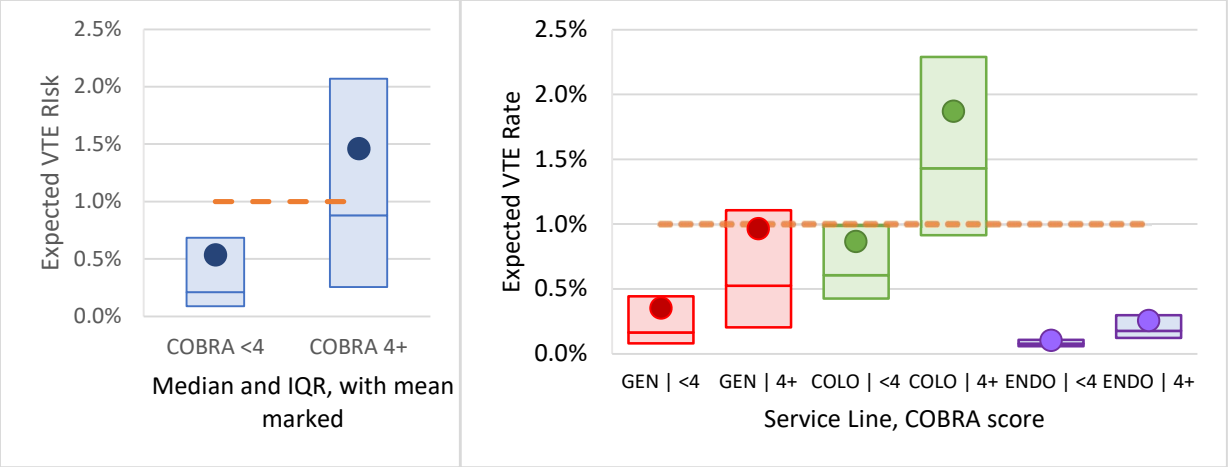


Figure 2 | Left: Discriminative performance of COBRA for sample of 10,711 Emory University Hospital Patients. Right: Comparison of discriminative capability of COBRA in three service lines, General (GEN), Colorectal (COLO), and Endocrine (ENDO) surgery.

inherently limited in its development and its application as elements were selected for inclusion merely due to their weights in other models, and the RAM was tested on single-institution samples.

This preliminary work inspired application of more rigorous statistical methods to the question of VTE risk assessment. In this investigation, we expand on this previous line of inquiry to explore whether pre-operatively available patient characteristics can be captured in a parsimonious model that is non-inferior to currently available models in the prediction of post-operative VTE in adult surgical patients. We thus have the following specific aims:

Aim 1: Derive a new prediction model for 30-day post-operative VTE that is highly usable, clinically pertinent, and non-inferior to the Caprini and ACS Risk Calculator models.

Hypothesis: It is possible to create a model that achieves an AUC within 0.05 of the ACS Risk Calculator and with improved sensitivity and specificity as compared to Caprini while capturing fewer variables than both.

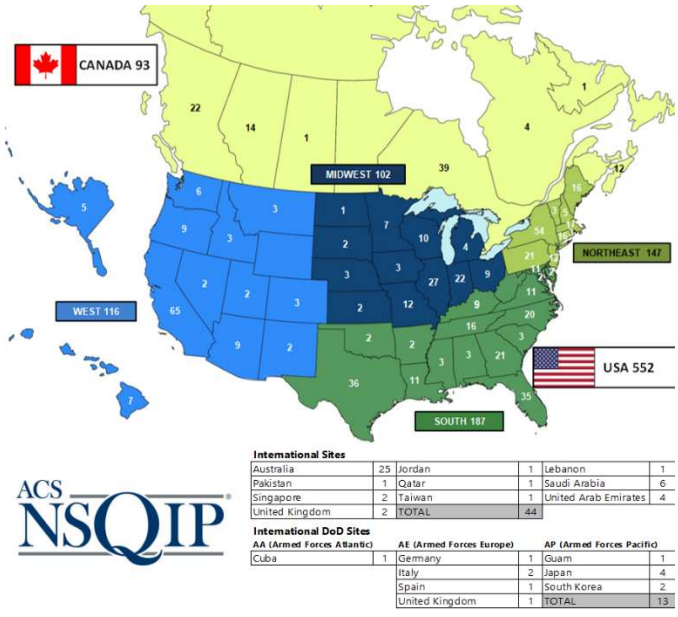
Aim 2: Explore rates of postoperative blood transfusions among different strata in the best performing model to provide data to inform the perception that bleeding risk is a barrier to VTE prophylaxis protocols.

2. Methods

2.1 Data Source and Study Population

The American College of Surgeons National Surgical Quality Improvement Project (NSQIP) originated in the Veterans Affairs Health System in 1991. In 2001, with support of the Agency for Healthcare Research and Quality, Emory participated in the piloting of this program in private sector hospitals. Today, to participate in NSQIP, hospitals designate a Surgeon Champion and Surgical Clinical Reviewers to abstract and submit data of 40 major cases every 8 days. This amounts to 1,800 cases per year, or about 16% of Emory's 11,000 annual cases. The only exclusion criteria for major cases submitted to NSQIP are age under 18 years and Trauma or Transplant surgery (as these are submitted to other well-defined national databases). This data has been collated, cleaned, and made available to participating sites for benchmarking and research since 2005 in the form of Public User Files (PUFs).

The NSQIP PUF dataset is a large and precise dataset that is the modern gold standard for surgical health services research. The total of roughly one million surgical patients included annually represent participation of ~700 hospitals across the United States and around the globe (Figure 3). Patients are represented in all major surgical fields, including General Surgery, Orthopedic Surgery, Obstetrics & Gynecology, Otolaryngology, Urology, Cardiothoracic Surgery, and the various subspecialties therein. The public user file contains upwards of 270 variables describing



International Sites					
Australia	25	Jordan	1	Lebanon	1
Pakistan	1	Qatar	1	Saudi Arabia	6
Singapore	2	Taiwan	1	United Arab Emirates	4
United Kingdom	2	TOTAL	44		

International DoD Sites					
AA (Armed Forces Atlantic)		AE (Armed Forces Europe)		AP (Armed Forces Pacific)	
Cuba	1	Germany	1	Guam	1
		Italy	2	Japan	4
		Spain	1	South Korea	2
		United Kingdom	1	TOTAL	13

Figure 3 | NSQIP participants by state, region, and country.

patients' demographics and comorbidities; elements of the pre-operative assessment; operative (CPT) codes; and post-operative outcomes within 30 days of the index operation.

Known limitations of the NSQIP PUF's external validity include over-representation of large (41% with >500 beds vs 23% of US hospitals[33]) and academic hospitals (31% vs 5% of US hospitals[34]). In addition to the non-random hospital selection, there is potential for non-random selection of cases for NSQIP submission which may also impart bias. While the internal validity of the data within is a strength of the PUF, there is no inclusion of process measures, which are the measurable steps that should be followed to provide high-quality care and that theoretically impact the outcomes of interest. Germane to this investigation, process measures such as ordering or administering VTE chemoprophylaxis, ordering and applying sequential compression devices, and measurement of post-operative mobility could provide a more comprehensive context to risk assessment and eventual VTE outcomes. This limitation is common in similar validation studies,[20] and marks a trade-off for the representativeness of such a large, international sample, as standard collection of these and other process measures is remarkably difficult. In an era where prophylaxis is standard of care, these process measures cannot ethically be randomly allocated prospectively. Furthermore, inclusion of some process measures without others introduces risks of confounding in regression modeling. So, for real-world feasibility of this project, we felt the PUF was the best available dataset to answer our research question.

The 2019 PUF was chosen for this investigation to avoid the impact of COVID-19 on outcomes in the 2020 and 2021 data, which is especially important given the hypercoagulability associated with the disease[35]. The 2019 NSQIP PUF includes 1,076,441 observations (i.e. patients) and 274 variables. We included all patients in the 2019 NSQIP Public User File (PUF) without exclusion. This study is exempt from formal institutional review board review as nonhuman subject research given that it utilizes a de-identified dataset.

2.2 Primary Outcome

VTE was defined by presence of either vein thrombosis requiring therapy or pulmonary embolus within 30 days of operation, as defined by NSQIP.[36] Per data abstraction instructions, the former must be a "new diagnosis of a venous thrombosis (superficial or deep), confirmed by a duplex, venogram, computed tomography (CT) scan, or any other definitive imaging modality (including direct pathology examination such as autopsy) AND the patient must [either] be treated [or have documented refusal of treatment]." The latter must be a "new diagnosis of a blood clot in the pulmonary artery [with] a ventilation-perfusion scan interpreted as high probability of pulmonary embolism or a positive CT exam, trans-esophageal echocardiogram, pulmonary arteriogram, CT angiogram, or any other definitive imaging modality (including direct pathology examination such as autopsy)."

This is a relatively narrow definition of VTE, as it excludes (1) clinically diagnosed events that are treated without definitive imaging and (2) the roughly 50% of VTE that remain subclinical as they never become symptomatic.[3,37,38] There is thus potential for misclassification of this primary outcome, although the former exclusion is relatively rare in today's practice, and the latter aligns with the project's goal of creating a clinically actionable model.

2.3 Data Cleaning and Establishing Variable Definitions

Data cleaning identified multiple needs to define variables for the planned analysis (SAS code for all newly defined variables is included as an Appendix). The primary outcome, VTE, was defined per above as a dichotomous variable using Boolean "or" logic connecting the two variables of vein thrombosis requiring therapy and pulmonary embolus, each of which was dichotomous as well. Age, which was initially coded as a character value to assign those patients older than 90 years a value of "90+", was recoded to a numeric variable where those patients were simply assigned the value of 90. BMI (with units of kg/m^2) was defined numerically by applying the standard calculation to the coded variables of height and weight. BMI was

subsequently categorized using standard nomenclature of normal weight, underweight, overweight, and three obesity classes as utilized by the Centers for Disease Control and Prevention (CDC).[39]

Two new variables were defined by parsing codified text in the PUF dataset. Diagnosed Cancer was defined as a dichotomous variable by parsing the ICD10 codes for inclusion of "*malignan*" (capturing *malignant* and *malignancy*), "*carcinoma*", or "*cancer*". The justification for and validation of this variable was previously described.[18] Minimally invasive surgery (MIS) was defined as a dichotomous variable by parsing the CPT codes for "*laparoscop*" or "*thoracoscop*" (capturing both *laparoscopic* and *laparoscopy*, etc.), allowing for differentiation of minimally invasive from open surgeries. Due to a combination of larger incisions, more post-operative pain limiting mobility, and selection bias of which patients require more invasive or exploratory surgeries, this differentiation was presumed *ab initio* to provide predictive value.[40,41]

Each of the previously defined RAMs that were to be used for comparison of performance was calculated from available variables. Each of the elements of COBRA – diagnosed cancer, age, BMI, race, and ASA-PS – was now present in the dataset (this RAM was created using NSQIP data[18]), so it was calculated precisely and a threshold of 4 was set as the threshold for intervention[32]. Caprini was estimated to the best approximation within the limitations of the NSQIP PUF dataset, as many of the requisite variables are not included.[42] All patients were assumed to have major surgery, as this is a criterion for inclusion in the NSQIP dataset, and additional points were assigned to patients undergoing hip or knee arthroplasty. Other variables that were used to assign points in this model were age, BMI, diagnosed cancer, history of congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD), and preoperative sepsis or pneumonia. A score of 5 in the Caprini model was defined as the threshold for intervention.

In response to previously identified limitations of available RAMs, we set the goal to have the newly derived model provide procedural specificity without sacrificing generalizability. The 2022 National Healthcare Safety Network Operative Procedure Code Map, a document used by the CDC, among others, for risk adjustment, was codified to assign CPT codes from the dataset to specific groups. The groupings in this document are defined by anatomical location and procedure type, an easily recognizable system to clinicians. Of 2492 CPT codes included in the PUF, 1599 were not initially included in the Code Map, and 332 of those had at least one VTE. We assigned CPT groupings to all codes that contributed at least 8 VTE or that were counted at least 1,079 times in the dataset, using an arbitrary cut-off of 0.1% of the total VTE or total study population, respectively, on the assumption that this would be a fair balance of inclusion and feasibility. Most were put into existing groups, but we also created new groups as needed: Arthroscopy, Cystectomy, Incision & Drainage, Plastic, Urologic, and Vascular; yielding a total of 45 CPT groups. The remaining 1541 CPT codes that were less contributory to both the overall sample size and the number of VTE were grouped as "Other" for feasibility sake, still accounting for a total of 102,945 patients (9.5% of the study population).

CPT Group	CPT Codes	Code Description
COLO	44140	Colectomy, partial; with anastomosis
COLO	44141	Colectomy, partial; with skin level cecostomy or colostomy
COLO	44143	Colectomy, partial; with end colostomy and closure of distal segment (Hartmann procedure)
COLO	44144	Colectomy, partial; with resection, with colostomy or ileostomy and creation of mucofistula
COLO	44147	Colectomy, partial; abdominal and transanal approach
COLO	44150	Colectomy, total, abdominal, without proctectomy; with ileostomy or ileoproctostomy
COLO	44155	Colectomy, total, abdominal, with proctectomy; with ileostomy
COLO	44160	Colectomy, partial, with removal of terminal ileum with ileocolostomy
COLO	44204	Laparoscopy, surgical; colectomy, partial, with anastomosis
COLO	44206	Laparoscopy, surgical; colectomy, partial, with end colostomy and closure of distal segment (Hartmann procedure)

Figure 4 | CPT Group Example. A selection from the Colorectal CPT group demonstrating the myriad CPT codes that describe colectomies. Codes 44204 and 44206 would also be marked as MIS due to the word "laparoscopy" in the description.

2.4 Covariates for VTE Risk Modeling

To facilitate future adoption into pre-operative workflows, we only included variables in the analysis that are normally evaluated pre-operatively, such as the demographic characteristics or known comorbidities. Demographics included age, race, ethnicity, and gender. Chronic comorbidities included BMI, functional status, ascites, bleeding disorder, CHF, COPD, diabetes, cancer, dyspnea, hypertension, smoking, chronic steroid use, weight loss of at least 10% over prior six months, and ventilator dependence. Pre-operative assessment characteristics included presence of wound infection or sepsis, transfusion requirement, acute renal failure, and ASA-PS class.

Exclusion criteria were developed with the goal of creating a clinically actionable model for pre-operative workflows: We excluded subjective and non-biological variables such as the patient's transfer status, whether the case was considered emergent, and whether the patient was inpatient or outpatient. We excluded provider surgical specialty given collinearity with CPT groups. We also excluded data that would not routinely be known in preoperative workflows, such as labs, in addition to the many intra- and post-operative variables included in the PUF.

2.5 Univariable and Bivariable Analyses

A complete case analytical approach was used for analysis. All data manipulation and analyses were conducted using SAS version 9.4 (SAS Institute Inc). Means and standard deviation are reported for normally distributed continuous variables. Non-normal continuous variables have median and interquartile range reported. *P* value threshold of 0.05 was used to define statistical significance unless otherwise noted.

Patients who sustained VTE were compared to all other patients in the NSQIP PUF. We performed bivariable analyses of each variable in the overall PUF population using chi-square testing and unadjusted simple or ordinal logistic regression for VTE outcomes. Age, specifically, was investigated as a continuous function and in 10- and 20-year increments to determine if

inflection points would necessitate an ordinal rather than continuous variable in the eventual regression model. We explored simplification of other ordinal variables that could be considered as dichotomous variables such as ASA-PS, diabetes, dyspnea, functional status, and sepsis. Missingness was explored for each of the original and newly defined variables as well.

As it was clear from univariable descriptive statistics in addition to prior research identifying the predictive capability of ASA-PS for VTE outcomes[18], we conducted bivariable logistic regression testing of candidate variables in combination with ASA-PS to get an *ab initio* sense of the additive value these variables may serve in a more complex model.

2.6 Logistic Regression Model Derivation

For model derivation, the dataset was randomly split into training (70%) and testing (30%) sets. We used a clinically-guided forward selection process to derive the multivariable model. Our preliminary covariate inclusion strategy held that included variables should be biologically feasible as conceptualized by a direct acyclic graph, have significant unadjusted OR for VTE outcomes, and be reasonably prevalent in the study sample. Cutoffs for unadjusted odds ratio for VTE outcomes, biological feasibility, and prevalence were created to assign point values that could be ascribed to each variable, creating a new composite appropriateness criteria for variable selection (Box 1). Once a preliminary model was formed, variables that did not meet these criteria were added sequentially with an alpha threshold of 0.01, chosen because the population was so large that alpha 0.05 did not discriminate any variables from the model.

Points	-1	0	1	2
Univariate association (OR)		1.0-1.2	1.2-1.5	>1.5
Biologically plausible (DAG)	misleading	no	maybe	yes
Prevalence (%)		0-2	2-5	5+

Box 1 | Point assignment protocol to identify candidate variables for model inclusion.

To refine the model further, we investigated potential interaction terms that had biological rationale, including: between age and sex, given the implications of estrogen concentrations on VTE risk; between age and ASA-PS, age and functional status, and cancer and

functional status to capture the clinical concept of frailty; and between BMI category and diagnosed cancer given the differing implications of weight loss on people with cancer. We performed sensitivity analyses to derive secondary models with more variables that may sacrifice eventual usability for predictive capability. Variable selection was conducted for these models by adjusting the threshold of the composite appropriateness criteria.

2.7 Model Performance

Model performance was measured by c-statistic, sensitivity and specificity for VTE outcomes. Two separate non-inferiority definitions were used, as the ACS Risk Calculator does not have a threshold for intervention. Non-inferiority to the ACS Risk Calculator was defined as c-statistic within 0.05 of the established standard of Bilimoria's 2013 model validation publication, in which the derived model was found to have a c-statistic of 0.819 for VTE outcomes.[30] Non-inferiority to COBRA and Caprini was defined as sensitivity and specificity equivalence using the respective predefined thresholds for intervention.

2.8 Scoring Model Building

Once a regression model was derived, we employed methods described by Bonnett *et al*[43] for developing a clinical risk score. These methods focus on assigning integer values to odds ratio ranges for variables in the regression model – including the transformation of continuous predictors into ordinal variables – and help navigate the "art" of making these integer values something that clinicians can easily capture, remember, and trust.

For the score to be clinically actionable, the next step was to choose a cut-off over which the model would identify a patient as being "high risk", and thus prompt the recommendation of chemoprophylaxis. Here sensitivity was valued over specificity, as for the clinical scenario in which the model would be used, the error of omission (in which a high-risk person is not given appropriate chemoprophylaxis and then sustains VTE) is much worse than the error of commission (in which a low-risk patient gets prophylactic heparin). Potential cut-off values

were discussed with clinical stakeholders, including review of potential clinical scenarios in which the model would or would not recommend prophylaxis.

Finally, the selected cut-off value evaluated in the testing dataset to determine its sensitivity and specificity for VTE outcomes, as well as the rates of VTE in the populations labelled as "high" and "low risk". These metrics of performance were compared to the same metrics using other model cut-offs in addition to the established high-risk thresholds in the Caprini and COBRA models.

2.9 Secondary Aim – Transfusion Requirement

The secondary outcome of postoperative blood transfusion was defined, per NSQIP, as the "transfusion of red blood cells, whole blood, autologous blood, and cell-saver products.... up to and including 72 hours from the surgical start time, postoperatively."[36] To explore the perceived risk and balance measure of bleeding as a barrier to consistent VTE prophylaxis, we compared relative rates of blood transfusions in patients stratified as high and low risk. This comparison was performed at different score thresholds of the new model and using the Caprini and COBRA models.

3. Results

3.1 Study Population

A total of 1,079,441 patients were included, of whom 7.6% sustained post-operative VTE and 4.1% required post-operative transfusion. Patients were on average 57 years of age (SD 17). 58% identified as female, 10% identified as Black or African American, and 66% identified as White. Forty-five percent were obese, 3% dependent at preoperative baseline, and 15% had diagnosed cancer. Baseline demographics and comorbidities are captured in Table 1.

3.2 Candidate Selection

Univariate regression modeling was performed for 29 variables that fit the general inclusion criteria of being reliably documented in pre-operative workflows, demonstrated in Table 2. Of all variables examined for potential inclusion, only race and ethnicity had substantial (>2%) missingness, with 20% and 19% missing, respectively. We did not find any inflection points in age as a continuous variable, and instead found a near-linear correlation between increasing age and VTE rate. Ordinal regression of age in 10- or 20-year increments demonstrated linear increases in resultant odds ratios, as demonstrated in the first "demographic" row of Table 2, so the decision was made to include age as a continuous variable in the multivariable logistic regression model.

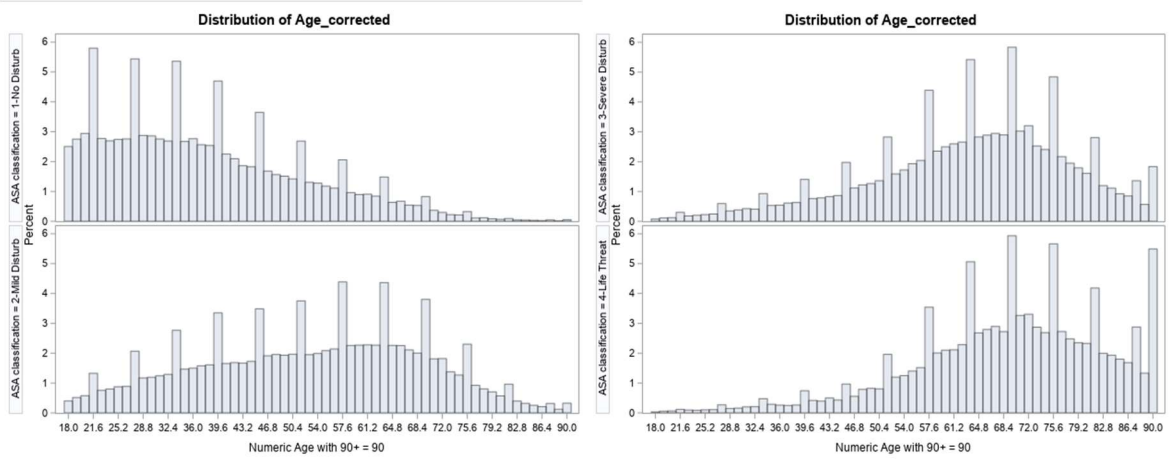


Figure 5| Distribution of age for patients with ASA-PS 1 (top left), 2 (bottom left), 3 (top right) and 4 (bottom right), demonstrating right skew in the first graph and left skew in all others. Provided as an example of the strong correlation of ASA-PS with other included variables.

As demonstrated in the first "comorbidity" row of Table 2, increasing ASA-PS had a near-exponential correlation with VTE outcomes. In fact, ASA-PS alone had a c-statistic for VTE outcomes of 0.650. Of twenty analyzed covariates, only age and disseminated cancer increased the c-statistic to 0.660 or higher in a bivariable model. A series of histograms demonstrate the distribution of age for patients with different ASA-PS scores in Figure 5. All included covariates had odds ratios nearer the null after adjustment for ASA-PS. Hypertension and BMI were no

longer statistically significant after adjustment. The BMI >25 threshold used in the Caprini model was insignificant as well.

Points were assigned to all included variables, with increasing point values for stronger univariate association, biological plausibility, and prevalence as demonstrated in Box 1. Point assignments are demonstrated in Table 3.

3.3 Regression Model Derivation and Performance

The clinically guided forward selection process identified six variables with five or more points that were used to create the foundational multivariable model: age, ASA-PS, BMI category, diagnosed cancer, sepsis, and MIS. All six variables were statistically significant upon regression, and c-statistic in the training dataset for this preliminary model was 0.706.

Sequential addition of other variables that scored four points identified five more statistically significant variables in the resultant model: functional status, ascites, steroids, transfusion, and CPT group. The c-statistic in the training dataset improved to 0.758 with inclusion of these variables.

Addition of lower scoring variables and interaction terms to the model only identified three more statistically significant variables: race, weight loss, and ventilator dependence. The resultant c-statistic improved to 0.761. As race had multiple reasons for not being included in the final model (discussed in Section 4.4) including substantial missingness, and as the model barely improved with the addition of these less clinically pertinent variables, the decision was made to proceed with the second (11-variable) model for testing. The final 11-variable model was found to have c-statistic of 0.753 in the testing dataset. Adjusted odds ratios for VTE outcomes for these 11 variables are included in Table 4.

Of note, both diabetes and smoking were statistically significant in the second and third regression models, but found to be protective (i.e. OR <1.0). As this does not align with inclusion

criterion of biological plausibility, these two variables were excluded from the final model (discussed in Section 4.3).

3.4 Risk Score Derivation and Performance

The final 11-variable regression model was used as the basis for developing a new risk score. To make the new model more memorable for CDS, first letters were taken from each of the included variables (with some manipulation of synonyms) to create a risk score name: **f**unctional status, **a**ge, **s**epsis, **t**ransfusion, **ASA-PS**, **s**teroids, **a**scites, **c**ancer, **l**aparoscopic (MIS), **o**besity, and **t**ype of surgery (CPT Group) became "FAST AS A CLOT".

Integer value points were assigned based on the adjusted odds ratios in the multivariable model, as demonstrated in Box 2, as follows: The ASA-PS score is taken as an integer value. Age is assigned 1, 2, or 3 points if over 30, 50, or 70 years, respectively. BMI greater than 35, functional dependence at baseline, and diagnosis of cancer each assign 1 point. Chronic steroid use, ascites, and pre-operative sepsis or transfusion requirement each assign 2 points. Each of 40 CPT groups is assigned a point value ranging from -2 to +4, and minimally invasive technique subtracts 2 points. The points assigned to each variable and CPT Group are demonstrated in Tables 4 and 5, respectively.

OR range	Points
1.0-1.5	1
1.5-2.0	2
2.0-3.0	3
>3.0	4

Box 2| Point assignments by odds ratio (OR) range in the adjusted model

The maximum number of points that could be counted for a specific patient would theoretically be 24. For example, this would apply to a 70-year-old (3), moribund (5) and dependent (1), obese (1) person who chronically takes steroids (2) and has known cancer (1) and ascites (2), who is currently septic (3) and requiring transfusion (2) prior to an open (0) colorectal (4) operation. The minimum number of points that could be assigned would be -1,

describing a young (0), otherwise healthy (1) person undergoing non-oncologic breast surgery (-2) or minimally invasive (-2) herniorrhaphy (0).

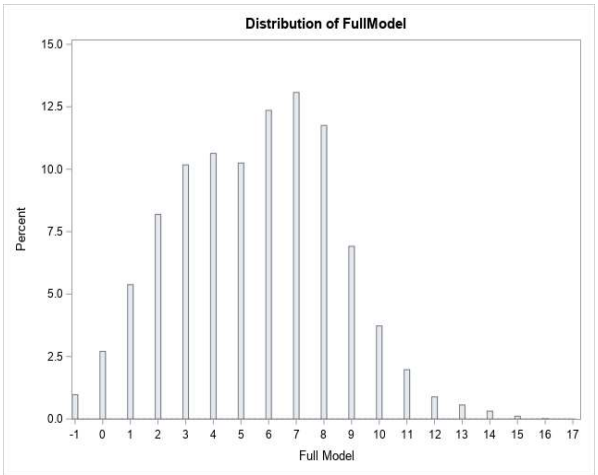


Figure 7 | Histogram of FAST AS A CLOT scores in the testing dataset.

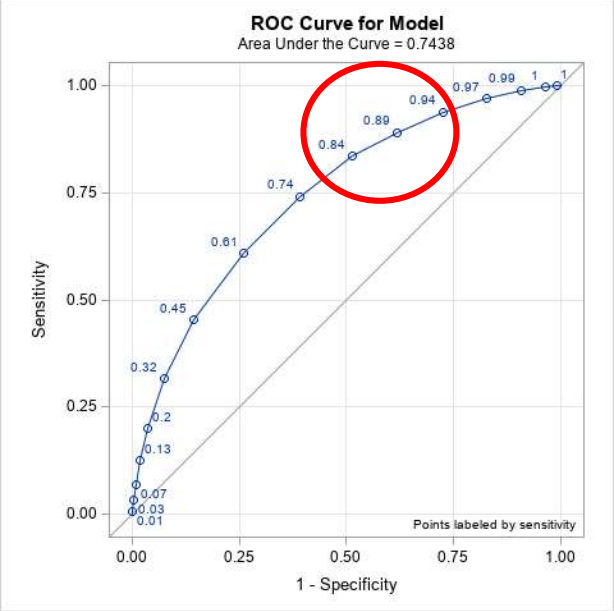


Figure 6 | Receiver operating curve of the FAST AS A CLOT model (c = 0.744), with three highly sensitive cut-off candidates circled.

In the testing dataset, the FAST AS A CLOT model yielded scores ranging from -1 to 17. These scores were slightly right-skewed, but generally normally distributed (Figure 6). The c-statistic diminished from 0.753 to 0.744 by simplifying the continuous regression model to integer values. Figure 7 demonstrates the receiver operating curve of FAST AS A CLOT with three highly sensitive cut-offs (corresponding to 4, 5, and 6 points) circled to demonstrate the focus of the model as a CDS tool. After discussion with clinician stakeholders, we decided that 5 points would be an appropriate high-risk cut-off. Table 6 demonstrates predictive performance of FAST AS A CLOT at these three potential cut-offs in addition to comparison with the COBRA and Caprini models.

3.5 Secondary Aim – Transfusion Requirements

Univariate analysis identified that those patients who sustained VTE had higher transfusion requirement than those who did not get VTE (18.2% vs 4.0%; relative rate 4.6). When stratifying patients into their VTE risk levels using FAST AS A CLOT, high VTE risk patients had a relative rate of transfusion requirement of 9.5 as compared to low VTE risk

patients (6.16% vs 0.65%). The alignment of high-VTE risk patients with high post-op transfusion rates was similarly seen at other cut-off values in the new model and in the COBRA and Caprini models, as demonstrated in Table 7.

4. Discussion

Multivariable logistic regression modelling with a clinically-guided forward selection process identified an 11-variable model that categorizes surgical patients as high or low risk for developing post-operative VTE. This model improves upon currently available RAMs in its being designed for pre-operative CDS.

To Specific Aim 1, the model's AUC fell below the predetermined threshold for non-inferiority in comparison to the ACS Risk Calculator, as the regression model c statistic of 0.753 is not within 0.05 of the 0.819 c-statistic identified in the 2013 ACS Risk Calculator validation study by Bilimoria *et al.*[30] The lower c-statistic is likely due to that (1) non-biological variables can actually be strongly predictive and that (2) the ACS Risk Calculator was validated ten years ago when prophylaxis rates were lower and thus it was potentially easier to achieve discrimination in a large dataset. While there remains a persistent gap across surgical care in proper consistent risk assessment and evidence-guided prophylaxis decisions, the rise in use of the ACS Risk Calculator and the Caprini model over the last decade have undoubtedly increased prophylaxis rates from where they were in 2013.[44] It is reasonable to assume that model performance would therefore be worse in 2019 data than in 2013 data, as high-risk patients would be more likely properly prophylaxed against this outcome. Validation studies of the Risk Calculator, Caprini, and other models have consistently identified C statistics between 0.7 and 0.8[20], so the performance of FAST AS A CLOT is well within generally accepted range of accuracy of other clinically accepted models.

In comparison to COBRA and Caprini, FAST AS A CLOT demonstrated improved sensitivity and wider differentiation of high from low risk. The specificity of FAST AS A CLOT was lower than that of the other models at the cut-off chosen, but a cut-off of 6 points would have had improved specificity (Table 6). Regarding clinical pertinence, the finding that the VTE rate of those identified as "high risk" is about 1% aligns with prior literature, as Le *et al* suggest that thromboprophylaxis is beneficial and cost-effective if a patient's VTE risk exceeds 1%[45].

To Specific Aim 2, this investigation identified that bleeding risk and VTE risk increase in parallel. Inclusion of pre-operative transfusion in the prediction of VTE clearly predisposed the resultant model to be strongly predictive of post-operative transfusion requirement. It is notable, though, that this trend was present in the Caprini and COBRA models as well. It is likely true that patients at risk for any morbidity are at risk for many morbidities; and clinicians should have heightened awareness of patient-level factors that predispose to post-operative complications in order to actively balance the risks and benefits of prophylactic anticoagulation.

4.1 Comparison to Available RAMs

The new FAST AS A CLOT model addresses many of the limitations of currently available RAMs. The variables included have more face validity and biological plausibility than many of those included in the ACS Risk Calculator, such as whether the planned case is emergent or whether the patient has hypertension. The resultant integer score and clearly defined intervention threshold are more actionable and understandable to clinicians and patients alike. Theoretically, the methodology of CPT grouping could include more CPT codes than those employed in the ACS Risk Calculator as well, although this would require further work as discussed below in Section 4.5. FAST AS A CLOT requires the capture of much fewer variables than the Caprini score, and yet inclusion of procedural specificity allows the new RAM to provide more generalizable decision support. Additionally, the methods employed in this study were much more rigorous than those employed in the development of the COBRA model.

4.2 Discussion of Specific Included Variables

The ASA-PS classification captures a global gestalt of the patient's systemic burden of disease.[31] It is an accurate independent predictor of post-operative morbidity and mortality in general[46], and of VTE in particular.[47,48] In accounting for multi-morbidity, it maintains collinearity with many risk factors that are used in RAMs such as the Caprini model. For example, while patients with COPD may indeed have higher rates of VTE, this is less likely causative than it is simply a marker of how sick someone is. As noted in Section 3.2, inclusion of this variable in a predictive model is thus highly efficient and accurate.[49]

In light of ASA-PS superseding so many other *correlative* variables, it is notable that steroid use and presence of ascites remained significant predictors even when adjusting for ASA-PS as these are not classically considered VTE risk factors. Both do have biologically plausible causative impact on VTE risk though: Studies show that that glucocorticoids increase levels of clotting factors and fibrinogen.[50,51] Glucocorticoid use has been connected to increased VTE risk in epidemiologic studies[52] and has a dose-response correlation to VTE risk in patients with asthma.[53] While similar studies have not been conducted in surgical patients, ulcerative colitis is an independent predictor of VTE in colorectal surgery patients[47] and is a risk factor in the Caprini score. Albumin is inherently antithrombotic.[54] Hypoalbuminemia is thus another independent predictor for VTE in surgical patients[47,48], and it is likely this in combination with coincident altered clotting factor concentrations that connects ascites to VTE risk.[55,56]

Age is ubiquitously used in VTE risk assessment models: The ACS Risk Calculator incorporates a linear regression of age, and Caprini has increasing points assigned to 40, 60, and 75 years similar to its use in FAST AS A CLOT. Age likely contributes to VTE risk due to a combination of decreased vessel elasticity, correlation with comorbidity burden, and as an implicit marker of frailty. A challenge of including age in RAMs is the increased risks of

anticoagulation in the elderly population as well as increased prevalence of chronic antiplatelet medications that might complicate decisions to prophylax.[57]

Functional status likely predicts VTE outcomes due to its correlation with mobility and frailty. In general, earlier and increased mobility decreases VTE risk.[15,58–60] Pre-operative functional status also strongly predicts post-operative functional decline.[61] Unfortunately, mobility in particular is a difficult process measure to capture in perioperative patients, and it is not captured in NSQIP databases. In light of the digital transformation of perioperative care, future research should aim to implement more standardized capture of mobility for risk assessment and real-time intervention.

Cancer contributes to VTE risk because of procoagulant and inflammatory cytokines, as well as the potential for patient immobilization, multiple surgical procedures, indwelling vascular catheters, and chemotherapy.[62,63] While it is included in most VTE RAMs, it can be challenging to capture cancer as a dichotomous variable for risk assessment. Given the many ways in which it can increase VTE risk, it is intuitive that metastatic high-grade malignancy would bestow more VTE risk than presence of or even history of low-grade local disease. However, very specific definitions like that of the Disseminated Cancer variable in the NSQIP PUF can exclude a large percentage of patients who have a cancer diagnosis and are thus at increased risk of VTE.[18] Given that the goal of a VTE RAM is to be highly sensitive to those at risk, a more liberal dichotomous variable must be employed[64], like the one used in FAST AS A CLOT. Caprini accomplishes this as well by including "present or previous malignancy."

As hypothesized (see Section 2.3), procedural specificity was essential to creating a highly predictive model, as both CPT Group and MIS were strongly significant. Other authors have found that open surgery is an independent predictor of VTE.[47] Indeed, practitioners often base their prophylaxis decisions on the type of procedure performed rather than patient comorbidities.[65] Interestingly, others have found that minor surgeries, head and neck

operations, mastectomy, and medical treatment are associated with overlooking anticoagulant administration, which may manifest in artificially high VTE rates in these low risk populations.[66] This is another topic where balance of sensitivity and specificity is key,[64] as identifying only the highest risk procedures runs the risk of being too specific in prophylaxis choices.[67]

Pre-operative transfusion requirement is an especially interesting discussion point because it underscores the multidimensional nature of chemoprophylaxis decision making. The association could be present due to an association with other comorbidities, because transfusion itself is pro-inflammatory[68], because pre-operative anemia and transfusions alter clotting factor composition, or because clinicians are hesitant to anticoagulate patients with transfusion needs. In any case, inclusion of this risk factor aligns with previous literature[48,69] and is clinically pertinent as it sheds light on a vulnerable population.

Obesity contributes to VTE risk by directly impacting hemostasis as well as indirectly by association with relative immobility and other contributory disease states such as cardiac disease.[70–72] As such, BMI is included in all VTE RAMs: Caprini incorporates a dichotomous variable using the cut-point of 25 kg/m^2, and the ACS Risk Calculator uses marginally increasing odds ratios for 30, 35, and 40 kg/m^2. This exemplifies that the difficulty with BMI lies in what cut-points to choose. In our data, there was an inflection point around BMI 30-35, so we selected BMI 35 as a cut-point for point assignment. However, this reasoning is limited in its biological plausibility. Further complicating this issue is that BMI is an imperfect estimation of adiposity and true impact of metabolic syndrome.[73] And finally, in the absence of process measure data, we cannot know whether obese patients were more likely to receive prophylaxis, thereby lessening the perceived impact of obesity on VTE outcomes. This limitation has led other authors to conclude that there is no association between obesity and VTE outcomes in other retrospective large database analyses.[74] This concept of non-random distribution of process measures is discussed at length in the following section.

4.3 Statistical Idiosyncrasies

Two statistical idiosyncrasies contributed to our findings. First, as previously noted, the higher BMI patients in the dataset may have been more likely to receive chemoprophylaxis than their lower BMI counterparts. Others have also found that with increased awareness of VTE risk associated with obesity, the higher adherence to prophylaxis in obese patients manifests in little if any increased rates of VTE.[75] The observation that presence of comorbidities may impact the documentation or delivery of standards of care is known as "paradoxical comorbidity".[76] In fact, many researchers have found that comorbidity can paradoxically improve outcomes.[77,78] In the derivation of FAST AS A CLOT, we found that hypertension and smoking were both *protective* against VTE. This is most likely due to higher quality care delivered to patients with these comorbidities overall, including improved compliance with VTE prophylaxis.

Second, rare outcomes pose a challenge in logistic regression models due to the imbalance of the data.[79,80] For example, in our dataset where the overall rate of VTE is less than 1%, a model that predicts zero VTE events will be more than 99% accurate, but the sensitivity of such a model is worthless to clinical practice. One solution to this problem is creating a matched control cohort where the sample size imbalance is less drastic. We elected not to do this because exclusion of a large proportion of the study population would contradict the goal to make a maximally generalizable model. Instead, we simply acknowledge that c-statistic alone is not an adequate measure of a RAM's clinical utility, and instead look forward to real-world validation, as discussed in Section 4.7.

4.4 Biological Plausibility and Face Validity

Biological plausibility and face validity were foundational in the derivation of FAST AS A CLOT, so much so that the development of the risk score prioritized these concepts above predictive accuracy. The decision to exclude race from the final model provides an important reflection of these themes.

There is a clear link between race and VTE prevalence.[81] In brief, this is likely due to a combination of socioeconomic and genetic factors, for which race is merely a proxy.[82,83] Acknowledging this, algorithms designed to be maximally *descriptive* should consider race data, especially in the absence of more granular metrics.[18,84,85] However, the use of the societal construct of race in a *prescriptive* algorithm – such as a RAM that provides CDS – has the potential to perpetuate inequities in care and outcomes.[86,87] Among the many ethical concerns this might raise is the question of who would determine race for use in such a model: I.e. if a patient's identity and the clinician's perception are discordant with respect to race, which would be considered in the assignment of points? The benefit of indirect proxy capture of socioeconomic factors that can impact patient health and hospital performance does not outweigh the cost of perpetuating inequities and losing face validity of the model.

In this way, race sits at the far end of a spectrum of non-biological or non-clinical variables the inclusion of which may improve predictive ability but at the cost of face validity. For example, whether or not a case is considered "emergent" is not inherently biological, but it does clearly correlate to how acutely sick a patient is and therefor their morbidity risk.[47,48] Similarly, a patient's having transferred from another facility inherently implies that their management was too complex for the initial facility to which they presented, and so correlates with acuity. Both of these are captured with variables in the NSQIP PUF and could be highly predictive of VTE, but were excluded from model derivation because it is hard to imagine a scenario where an algorithm directs a prophylaxis decision because a patient was transferred from another facility. As a counter example, functional status is not completely biological. However, it was deemed appropriate for inclusion based on the aforementioned presumed association with mobility, which does have biological association with VTE.

4.5 Study limitations

This study has multiple limitations. Methodologically, the study is limited in its reliance on one year's sample within one retrospective database. The NSQIP PUF also has multiple limitations itself, as presented in Section 2.1. The methods employed could be refined with more robust CPT grouping. As discussed in Section 2.3, the cut-off for grouping of 0.1% of the sample left over 1500 codes ungrouped, which represents a total of ~10% of the study population. The decision to group CPT codes was in response to the limitation presented in Bilimoria's ACS Risk Calculator verification study[30], in which codes with a prevalence less than 200 in their sample were excluded. Meeting this standard would require assignment of 290 more codes to CPT groups. Importantly, this would not be a one-time workflow. If this model were to be automated, there would have to be a fairly regular review process to confirm that routinely used codes are assigned to groups, as CPT code usage is not necessarily consistent over time.

In light of the previous section, the FAST AS A CLOT model is, philosophically, not entirely predictive nor entirely causative. The model was designed with causative logic in mind, as the inclusion of specific variables was reliant on biological plausibility and face validity. However, with this inclusion criteria, we aimed to maximize predictive capability as a measure of success of Aim 1. Predictive performance could have been improved by including more variables and by de-emphasizing the concepts of plausibility. We acknowledge that there is a degree of subjectivity in these inclusion criteria.

There are also limitations of VTE as a performance indicator overall. Unlike other key performance indicators like pneumonia or surgical site infection, methods for detection of VTE remain inconsistent. There is no standard screening method for VTE; there is well-described surveillance bias at centers that have high rates of prophylaxis adherence[88]; and studies that have instituted screening for VTE have identified markedly higher rates than those reported in quality databases.[38] Further complicating the variable detection rate is the challenge that

appropriate prophylaxis does not avoid all VTE. In fact, many patients who receive appropriate prophylaxis go on to sustain VTE.[89,90] We still do not truly know the end goal for VTE prevention, but zero VTE does not seem feasible.

4.6 Future Research Opportunities

Further pre-clinical validation of the FAST AS A CLOT model could be performed if needed for stakeholder buy-in. This could be performed using similar methods in either other years of the NSQIP PUF or other datasets altogether. Regarding the first option, preliminary investigation of other years datasets found consistency in which procedures contribute most to the system-wide burden of VTE,[91] so we would not expect to derive a drastically different RAM using other years' data. Using other datasets that include prophylaxis information and other process measures could account for a foundational limitation of this project and the ACS Risk Calculator. Propensity score matching in this type of dataset may allow for calculation of a treatment effect of chemoprophylaxis and control for this effect in further analysis. Datasets that are both detailed enough to support this type of analysis and large enough to provide statistical power and generalizability are not readily available.

Within the development of novel RAMs, one exciting horizon is in models that attempt to balance clotting and bleeding risks, which have been developed in some specific populations.[21] If validated, these two-outcome models could clarify the challenging conclusion of this study and many clinical practice guidelines that after all risk assessment is performed it is up to the surgeon to balance the competing risks of clotting and bleeding.

Going beyond the scope of VTE risk assessment, there are many more research questions within the field of perioperative VTE prophylaxis: This study's scope is limited to dichotomously risk-stratifying patients, without delving into the many details of chemoprophylaxis such as medication choice, timing of initiation, interval between doses, duration of therapy, etc. There is

tremendous variability in these practices across surgical specialties and practice settings, which is the focus of an ongoing scoping review.

4.7 Implementation

For a derived model to impact outcomes, it must be implemented into patient care. CDS interventions that are trusted and adopted have the power to dramatically improve VTE prophylaxis adherence and VTE incidence.[15] In their chapter on "Using practice guidelines to improve patient care," the authors of *Optimal Resources for Surgical Quality and Safety* ("the Red Book") encourage deploying a "shared baseline protocol" in which the new guideline is blended into clinical workflows without relying on human memory or new decision points.[92] They emphasize the need for implementation despite limitations, avoiding the aim of perfection.

The first step towards implementation is to calculate FAST AS A CLOT within the electronic health record (EHR). Emory has used the Epic® EHR since 2022. Epic allows Clinician Builders the functionality of creating custom calculations. The custom calculation will automatically pull in documented, codified information such as age, BMI, and ASA-PS. Capturing other variables like sepsis, ascites, and functional status will require the design of a custom flowsheet rows. Future iterations of the build could embed logic such as automatically pulling cancer diagnoses from the problem list, connecting with blood bank documentation to capture pre-operative transfusions, or pulling CPT codes from the case schedule. A new SmartForm will be built to house the custom calculation and embed it into History & Physical note templates.

Validation of the model can be done prospectively in clinical care.[93] Prospective evaluation is relatively easy to accomplish once built into the EHR and beta tested for functionality. The first stage of this process would be calculating the FAST AS A CLOT score on a small pilot population without providing the subsequent CDS. This stage would serve as a confirmation of clinical appropriateness and functionality in real-time. The second stage would

be to conduct a prospective pilot with a selection of surgeons or service lines. Per best practices[12], the surgeon would receive an alert of their patient's VTE risk level with guidelines for prophylaxis choices included. In each of these first two stages, a comparison to the Caprini model would be performed to confirm relative alignment. The third stage would be to default prophylaxis choices or prompt CDS based on an automated score. This requires a higher threshold of trust in the RAM, which would need to be developed in the preceding stages. Taking best practices again from the Red Book, variance from the encouraged practice should be tracked throughout each stage, analyzed for iterative refinement of the guideline, and communicated back to clinicians and other stakeholders in real-time.[92]

5. Conclusion

VTE remains a leading preventable cause of perioperative morbidity and mortality, in part due to lack of consistent, standardized risk assessment. Our goal was to derive a new VTE RAM that addresses the limitations of currently available models. Using multivariable logistic regression modeling with a clinically-guided forward selection process, we developed a model that is both parsimonious and procedurally specific, that is designed to have face validity to clinicians and fit in their workflows, and that provides actionable risk stratification. By implementing this RAM, we hope to increase preoperative prophylaxis guideline adherence and decrease the rate of VTEs, thereby improving the health outcomes of post operative patients.

6. Tables

Table 1: Demographics, comorbidities, and pre-operative care characteristics of patients who did and did not sustain post-operative VTE in the 2019 NSQIP PUF.

Variable	**No VTE** **N = 1,068,280**	**VTE** **N = 8,161**	**Total** **N = 1,079,441**
Demographics, n (%)			
Age group, years			
Younger than 30	85,169 (8.0)	202 (2.5)	85,371 (8.0)
30-40	116, 196 (10.9)	470 (5.8)	116,666 (10.8)
40-50	146,996 (13.8)	801 (9.8)	147,797 (13.7)
50-60	197,906 (18.5)	1,385 (17.0)	199,291 (18.5)
60-70	248,022 (23.2)	2,112 (25.9)	250,134 (23.2)
70-80	189,313 (17.7)	2,062 (25.3)	191,375 (17.8)
Older than 80	84,675 (7.9)	1,129 (13.8)	85,804 (8.0)
Race			
White	706,521 (66.1)	5,449 (66.8)	711,970 (66.1)
Black or African American	101,633 (9.5)	1,021 (12.5)	102,654 (9.5)
Asian	34,829 (3.3)	154 (1.9)	34,983 (3.3)
American Indian or Alaska Native	5,356 (0.5)	40 (0.5)	5,396 (0.5)
Native Hawaiian or Pacific Islander	3,520 (0.3)	16 (0.2)	3,536 (0.3)
Unknown / Not Reported	216,421 (20.3)	1,481 (18.2)	217,902 (20.2)

Variable	**No VTE** **N = 1,068,280**	**VTE** **N = 8,161**	**Total** **N = 1,079,441**
Ethnicity			
Hispanic	94,436 (8.8)	523 (6.4)	94,959 (8.8)
Not Hispanic	771,180 (72.2)	6,235 (76.4)	777,415 (72.2)
Unknown	202,664 (19.0)	1,403 (17.2)	204,067 (19.0)
Sex			
Female	617,543 (57.8)	4,262 (52.2)	621,805 (57.8)
Male	450,618 (42.2)	3,899 (47.8)	454,517 (42.2)
Non-Binary	119 (0.0)	0 (0.0)	119 (0.0)
Comorbidities, n (%)			
ASA-PS Class			
1 – No Disturbance	84,969 (8.0)	175 (2.1)	85,144 (7.9)
2 – Mild Disturbance	484,352 (45.3)	2,117 (25.9)	486,469 (45.2)
3 – Severe Disturbance	437,959 (41.0)	4,556 (55.8)	442,515 (41.1)
4 – Life-Threatening	56,732 (5.3)	1,218 (14.9)	57,950 (5.4)
5 – Moribund	1,821 (0.2)	84 (1.0)	1,905 (0.2)
None Assigned	2,447 (0.2)	11 (0.1)	2458 (0.2)
Functional Status			
Independent	1,034,667 (96.9)	7,615 (93.3)	1,042,282
Partially Dependent	21,155 (2.0)	393 (4.8)	(96.8)
Totally Dependent	4,175 (0.4)	93 (1.1)	21,548 (2.0)
Unknown	8,283 (0.8)	60 (0.7)	4,268 (0.4)
			8,343 (0.8)
Ascites	2,786 (0.3)	100 (1.2)	2,886 (0.3)

Variable	No VTE N = 1,068,280	VTE N = 8,161	Total N = 1,079,441
Bleeding Disorder	37,740 (3.5)	618 (7.6)	38,358 (3.6)
BMI category			
Underweight	15,189 (1.5)	169 (2.1)	15,358 (1.5)
Normal	231,502 (22.2)	1,739 (22.0)	233.241 (22.2)
Overweight	329,326 (31.6)	2,358 (29.8)	331,684 (31.5)
Obesity – Class I	241,076 (23.1)	1,785 (22.6)	242,861 (23.1)
Obesity – Class II	127,331 (12.2)	1,029 (13.0)	128,360 (12.2)
Obesity – Class III	99,272 (9.5)	821 (10.4)	100,093 (9.5)
Missing	24,584	260	24,844
CHF	8,879 (0.8)	172 (2.1)	9,051 (0.8)
COPD	42,701 (4.0)	589 (7.2)	43,290 (4.0)
Diabetes			
Insulin	55,997 (5.2)	592 (7.3)	56,589 (5.3)
Non-Insulin	105,741 (9.9)	948 (11.6)	106,689 (9.9)
Dialysis	11,280 (1.1)	179 (2.2)	11,459 (1.1)
Disseminated Cancer	24,025 (2.3)	695 (8.5)	24,720 (2.3)
Diagnosed Cancer	161,114 (15.1)	1,951 (23.9)	163,065 (15.2)
Dyspnea			
At Rest	3,273 (0.3)	61 (0.8)	3,334 (0.3)
With Moderate Exertion	53,117 (5.0)	674 (8.3)	53,791 (5.0)
Hypertension	462,063 (43.3)	4,457 (54.6)	466,520 (43.3)
Smoker	164,335 (15.4)	1,216 (14.9)	165,551 (15.4)
Steroid Use (Chronic)	38,283 (3.6)	681 (8.3)	38,964 (3.6)

Variable	**No VTE** **N = 1,068,280**	**VTE** **N = 8,161**	**Total** **N = 1,079,441**
Weight Loss >10% in 6 Months	12,732 (1.2)	417 (5.1)	13,149 (1.2)
Ventilator Dependent	2,603 (0.2)	216 (2.7)	2,819 (0.3)
Pre-Operative Care, n (%)			
Transfer			
From Outside ED	19,268 (1.8)	410 (5.0)	19,678 (1.8)
From Acute Care Inpatient	16,037 (1.5)	399 (4.9)	16,436 (1.5)
From Nursing Home	8,354 (0.8)	160 (2.0)	8,514 (0.8)
From Other	3,705 (0.4)	60 (0.7)	3,765 (0.4)
Admit from home (not transferred)	1,017,876 (95.3)	7,118 (87.2)	1,024,994
Unknown	3,040 (0.3)	14 (0.2)	(95.2) 3,054 (0.3)
Emergent Case	96,180 (9.0)	1,377 (16.9)	97,557 (9.1)
Inpatient Status (vs Outpatient)	593,828 (55.6)	7,017 (86.0)	600,845 (55.8)
Renal Failure, Acute	3,212 (0.3)	81 (1.0)	3,293 (0.3)
Sepsis Pre-op			
SIRS	34,212 (3.2)	578 (7.1)	34,790 (3.2)
Sepsis	19,509 (1.8)	474 (5.8)	19,983 (1.9)
Septic Shock	3,564 (0.3)	264 (3.2)	3,828 (0.4)
Transfusion Pre-op	7,699 (0.7)	300 (3.7)	7,999 (0.7)
Wound Infection Pre-op	19,344 (1.8)	310 (3.8)	19,654 (1.8)

Variable	**No VTE** **N = 1,068,280**	**VTE** **N = 8,161**	**Total** **N = 1,079,441**
Surgical Specialty			
General	436,804 (40.9)	3,515 (43.1)	440,319 (40.9)
Cardiac	4,196 (0.4)	55 (0.7)	4,251 (0.4)
Gynecology	110,554 (10.4)	398 (4.9)	110,952 (10.3)
Interventional Radiology	81 (0.0)	1 (0.0)	82 (0.0)
Neurosurgery	58,112 (5.4)	802 (9.8)	58,914 (5.5)
Obstetrics	11,549 (1.1)	18 (0.2)	11,567 (1.1)
Orthopedics	269,242 (25.2)	2,155 (26.4)	271,397 (25.2)
Otolaryngology	25,265 (2.4)	65 (0.8)	25,330 (2.4)
Plastics	31,939 (3.0)	109 (1.3)	32,048 (3.0)
Thoracic	12,272 (1.1)	174 (2.1)	12,446 (1.2)
Urology	64,642 (6.1)	487 (6.0)	65,129 (6.1)
Vascular	43,624 (4.1)	382 (4.7)	44,006 (4.1)

Table 2: Univariable logistic regression modeling of VTE outcomes in the 2019 NSQIP PUF.

Variable	Crude OR (CI)
Demographics	
Age group, years	
Younger than 30	Ref
30-40	1.71 (1.45-2.01)
40-50	2.30 (1.97-2.68)
50-60	2.95 (2.55-3.42)
60-70	3.59 (3.11-4.15)
70-80	4.59 (3.97-5.31)
Older than 80	5.62 (4.84-6.53)
Race	
White	Ref
Black or African American	1.30 (1.22-1.39)
Asian	0.57 (0.49-0.67)
American Indian or Alaska Native	0.97 (0.71-1.32)
Native Hawaiian or Pacific Islander	0.59 (0.36-0.96)
Unknown / Not Reported	0.89 (0.84-0.94)
Ethnicity	
Hispanic	0.69 (0.63-0.75)
Not Hispanic	Ref
Unknown	0.86 (0.81-0.91)

Variable	**Crude OR (CI)**
Sex, n (%)	
Female	Ref
Male	1.25 (1.20-1.31)
Non-Binary	Excluded
Comorbidities	
ASA-PS Class	
1 – No Disturbance	Ref
2 – Mild Disturbance	2.12 (1.82-2.48)
3 – Severe Disturbance	5.05 (4.34-5.88)
4 – Life-Threatening	10.42 (8.89-12.22)
5 – Moribund	22.40 (17.20-29.17)
None Assigned	2.18 (1.19-4.02)
Dependent Functional Status	2.61 (2.38-2.86)
Ascites	4.75 (3.89-5.80)
Bleeding Disorder	2.24 (2.06-2.43)
BMI category	
Underweight	1.48 (1.26-1.74)
Normal	REF
Overweight	0.95 (0.90-1.01)
Obesity – Class I	0.99 (0.92-1.05)
Obesity – Class II	1.08 (1.00-1.16)
Obesity – Class III	1.10 (1.01-1.20)
CHF	2.57 (2.21-2.99)
COPD	1.87 (1.72-2.03)

Variable	**Crude OR (CI)**
Diabetes	
Insulin	1.45 (1.33-1.58)
Non-Insulin	1.23 (1.15-1.31)
Dialysis	2.10 (1.81-2.44)
Disseminated Cancer	4.05 (3.74-4.38)
Diagnosed Cancer	1.77 (1.68-1.86)
Dyspnea	1.78 (1.65-1.92)
Hypertension	1.58 (1.51-1.65)
Smoker	0.96 (0.91-1.02)
Steroid Use (Chronic)	2.45 (2.26-2.65)
Weight Loss >10% in 6 Months	4.47 (4.04-4.94)
Ventilator Dependent	11.14 (9.68-12.82)
Pre-Operative Care	
Sepsis Pre-op	
SIRS	2.50 (2.29-2.72)
Sepsis	3.59 (3.27-3.94)
Septic Shock	10.94 (9.64-12.43)
Renal Failure, Acute	3.33 (2.67-4.15)
Transfusion Pre-op	5.26 (4.68-5.91)
Wound Infection Pre-op	2.14 (1.91-2.40)
Transfer	3.11 (2.91-3.32)
Emergent Case	2.05 (1.94-2.18)
Inpatient Status (vs Outpatient)	4.90 (4.60-5.22)

Variable	**Crude OR (CI)**
Surgical Specialty	
General	Ref
Cardiac	1.63 (1.25-2.13)
Gynecology	0.45 (0.40-0.50)
Interventional Radiology	1.53 (0.21-11.03)
Neurosurgery	1.72 (1.59-1.85)
Obstetrics	0.19 (0.12-0.31)
Orthopedics	1.00 (0.94-1.05)
Otolaryngology	0.32 (0.25-0.41)
Plastics	0.42 (0.35-0.51)
Thoracic	1.76 (1.51-2.05)
Urology	0.94 (0.85-1.03)
Vascular	1.09 (0.98-1.21)

Table 3: Point values assigned to each variable for clinically guided forward selection process.

	Univariate association [A]	Biologically plausible [B]	Prevalence [C]	Overall
Demographics				
age	2	2	2	6
race	1	1	1	3
ethnicity	0	0	2	2
sex	1	1	2	4
Comorbidities				
ASA-PS Class	2	2	2	6
functional status	2	1	1	4
ascites	2	2	0	4
bleeding disorder	2	1	1	4
BMI category	1	2	2	5
CHF	2	2	0	4
COPD	2	1	1	4
diabetes	1	0	2	3
dialysis	2	1	0	3
diagnosed cancer	2	2	2	6
dyspnea	2	0	2	4
hypertension	2	0	2	4
sepsis pre-op	2	2	1	5
smoker	0	1	2	3
steroid use	2	1	1	4

renal failure	2	1	0	3
transfusion pre-op	2	2	0	4
weight loss >10%	2	1	0	3
wound infection	2	1	0	3
ventilator dependent	2	1	0	3
Pre-operative care				
Transfer	2	-1	1	2
Emergent case	2	-1	2	3
inpatient status	2	-1	2	3
surgical specialty	2	-1	2	3
CPT Group	2	1	1	4
minimally invasive (MIS)	2	1	2	5

[A] 0 points for odds ratio (OR) 1.0-1.2, 1 point for OR 1.2-1.5, 2 points for OR > 1.5

[B] -1 point for misleading association, +1 for possible biological association, +2 for clear biological association

[C] 0 points for sample prevalence <2%, 1 point for prevalence 2-5%, 2 points for prevalence > 5%

Table 4: Multivariable logistic regression modeling of VTE outcomes in the 2019 NSQIP dataset and subsequent integer value points assigned for the newly derived risk score.

Variable	Adjusted OR (95% CI)	Points Assigned
Age	1.011 (1.009-1.013)	1, 2, 3, if >30, >50, >70
ASA-PS (vs. 1)		ASA-PS Score
2	1.361 (1.117-1.657)	
3	2.019 (1.653-2.465)	
4	2.556 (2.060-3.173)	
5	2.066 (1.422-3.001)	
Functionally Dependent	1.425 (1.103-1.841)	1
BMI (vs Normal)		
Underweight	0.916 (0.753-1.113)	
Overweight	1.030 (1.011-1.175)	
Mild Obesity	1.166 (1.075-1.264)	
Moderate Obesity	1.257 (1.142-1.384)	1 if BMI > 35
Morbid Obesity	1.269 (1.141-1.411)	
Diagnosed Cancer	1.504 (1.383-1.634)	1
Steroid use	1.617 (1.465-1.784)	2
Ascites	1.785 (1.386-2.299)	2
Transfusion	1.728 (1.477-2.021)	2
Sepsis		3 (for all)
SIRS	2.194 (1.959-2.457)	
Sepsis	2.652 (2.326-3.024)	
Septic Shock	3.762 (3.120-4.573)	

MIS	0.575 (0.524-0.631)	-2
CPT Group*		
Breast	0.419 (0.324-0.540)	-2
Cholecystectomy	0.986 (0.774-1.256)	0
Arthroscopy	1.216 (0.967-1.528)	1
Hysterectomy	1.577 (1.304-1.908)	2
Thoracic	2.058 (1.570-2.698)	3
Colorectal	3.263 (2.802-3.799)	4

* Examples selected to demonstrate range of values.

Table 5: CPT group point assignments for the FAST AS A CLOT model.

Points	CPT Groups	
-2	Breast	Thyroid
	Cesarean section	Carotid endarterectomy
-1	Urology	
0	Herniorrhaphy	Incision & Drainage
	Appendectomy	Ovarian
	Cholecystectomy	Vaginal Hysterectomy
1	Arthroscopy	Neck Dissection
	Amputation	
2	Hip or Knee Arthroplasty	Laminectomy
	Abdominal Hysterectomy	Open Vascular
3	Abdominal Aortic Aneurysm	Femur Fixation
	Cardiac	Nephrectomy
	Thoracic	Prostatectomy
	Spinal Fusion	Exploratory Laparotomy
4	Hepatobiliary	Gastrectomy
	Colorectal	Plastic Reconstructive
	Craniectomy	Splenectomy
	Cystectomy	

Table 6: Sensitivity and specificity for VTE outcomes of the FAST AS A CLOT model at three cut-offs considered (5 was chosen for implementation). Performance is compared to Caprini and COBRA models.

Model	Cut-off	Sensitivity	Specificity	VTE rate (%), High risk	VTE rate (%), Low risk	RR VTE
FAST AS A CLOT	4	.938	.276	0.97	0.17	5.7
FAST AS A CLOT	**5**	**.890**	**.383**	**1.08**	**0.22**	**4.9**
FAST AS A CLOT	6	.836	.486	1.22	0.26	4.7
COBRA	4	.768	.456	1.06	0.38	2.8
Caprini [A]	5	.617	.532	0.97	0.53	1.8

[A] Caprini estimated using procedure type, age, BMI, diagnosed cancer, history of CHF or COPD, and preoperative sepsis or pneumonia.

Table 7: Post-operative transfusion rates of those patients classified as high and low risk in each model.

Model	Cut-off	Transfusion rate (%), High VTE risk	Transfusion rate (%), Low VTE risk	RR Transfusion
FAST AS A CLOT	4	5.40	0.52	10.4
FAST AS A CLOT	**5**	6.16	0.65	9.5
FAST AS A CLOT	6	7.02	0.90	7.8
COBRA	4	6.16	1.56	3.9
Caprini [A]	5	5.45	2.63	2.1

[A] Caprini estimated using procedure type, age, BMI, diagnosed cancer, history of CHF or COPD, and preoperative sepsis or pneumonia.

7. Appendix: SAS Variable Definitions

Age Numeric (AGE_Corrected)

```
IF Age = '90+' THEN Age_corrected = 90;
    ELSE Age_corrected = Age;
```

BMI

```
IF WEIGHT = -99 THEN WEIGHT = .;
    IF HEIGHT = -99 THEN HEIGHT = .;
    BMI = 703*(WEIGHT/HEIGHT**2);
```

Diagnosed Cancer

If post-op ICD9 or ICD10 diagnosis text contains “malignan”, “carcinoma”, or “cancer” OR If Disseminated Cancer = Yes → Yes

COBRA

Laymen’s terms:

Diagnosed Cancer: Yes = 1, No = 0

Age Numeric: ≥60 = 1, <60 = 0

BMI ≥30 = 1, <30 = 0

Race: Black or African American = 1, else = 0

ASA-PS

```
COBRA = Diagnosed_Cancer;
        IF Age_corrected >= 60 THEN COBRA = COBRA + 1;
```

```
                IF BMI >= 30 THEN COBRA = COBRA + 1;

                IF RACE_NEW = 'Black or African American' THEN COBRA = COBRA +
    1;

                IF ASACLAS = '1-No Disturb' THEN COBRA = COBRA + 1;

                IF ASACLAS = '2-Mild Disturb' THEN COBRA = COBRA + 2;

                IF ASACLAS = '3-Severe Disturb' THEN COBRA = COBRA + 3;

                IF ASACLAS = '4-Life Threat' THEN COBRA = COBRA + 4;

                IF ASACLAS = '5-Moribund' THEN COBRA = COBRA + 5;
```

COBRA Risk

```
    IF COBRA >=4 THEN COBRA_Risk = 'High';

    ELSE COBRA_Risk = 'Low';
```

Caprini AND Caprini Risk

```
    Caprini = 2;     *Assuming all pts are getting >45 min and/or arthroscopic surgery;

                IF Age_corrected >= 41 THEN Caprini = Caprini + 1;

                        IF Age_corrected >= 61 THEN Caprini = Caprini + 1;

                        IF Age_corrected >= 75 THEN Caprini = Caprini + 1;

                IF BMI > 25 THEN Caprini = Caprini + 1;

                IF Diagnosed_Cancer = 1 THEN Caprini = Caprini + 2;

                IF HXCHF = 1 THEN Caprini = Caprini + 1;

                IF PRSEPIS = 1 THEN Caprini = Caprini + 1;
```

```
                IF HXCOPD = 1 THEN Caprini = Caprini + 1;

                IF PNAPATOS = 1 THEN Caprini = Caprini + 1;

                LABEL Caprini = 'Estimated Caprini Score';

        IF Caprini >=5 THEN Caprini_Risk = 'High';

                ELSE Caprini_Risk = 'Low';

                LABEL Caprini_Risk = 'High if >=5';
```

VTE (primary outcome)

```
        IF (OTHDVT = 'DVT Requiring Therapy' or PULEMBOL = 'Pulmonary Embolism')
        THEN VTE = 1;

        ELSE VTE = 0;
```

MIS (minimally invasive technique, i.e. laparoscopic or thoracoscopic)

```
        if index(Description,'laparoscop')>0 then MIS = 1;

            else if index(Description,'Laparoscop')>0 then MIS = 1;

            else if index(Description,'thoracoscop')>0 then MIS = 1;

            else if index(Description,'Thoracoscop')>0 then MIS = 1;

            else MIS = 0;
```

8. Disclosure

Neither the author nor either advisor has any relevant conflicts of interest. The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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