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Venous thromboembolism and transfusion after major abdominopelvic surgery

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ABSTRACT

Background: Thromboprophylaxis aims to reduce venous thromboembolism but has the potential to increase bleeding. We sought to evaluate the risk of venous thromboembolism and transfusion after major abdominopelvic procedures and to quantify the association of the procedure with venous thromboembolism.
Methods: The American College of Surgeons' National Surgical Quality Improvement Program was queried for patients who received an abdominopelvic surgery between 2005 and 2016. Patient factors, operative factors, and outcomes were collected. Multivariable analyses were used to determine the association between individual procedures and venous thromboembolism. Area under the curve analyses were performed to assess whether addition of the procedure to Caprini score improved the association of the model with venous thromboembolism. The primary outcome was risk of venous thromboembolism within 30 days of surgery. Secondary outcomes were the risk of transfusion within 30 days and the association between operative time with venous thromboembolism.
Results: There were 896,441 patients who received an abdominopelvic procedure. The overall risk of venous thromboembolism was 1.9% (n = 16,665). Procedures with the highest risk of venous thromboembolism were esophagectomy (5.5%) and partial esophagectomy (5.3%). The overall risk of transfusion was 9.5% (n = 84,889). Procedures with the highest risk of transfusion were pelvic exenteration (53.6%) and radical cystectomy (37.7%). On multivariable analyses, individual procedures were independently associated with venous thromboembolism, despite adjusting for Caprini score. Area under the curve analyses indicated risk prediction of the baseline model (area under the curve 0.59) improved when procedures were added (area under the curve 0.68).
Conclusion: Patients undergoing abdominopelvic surgery are at a high risk of venous thromboembolism and transfusion. Improved risk stratification may be possible by including more procedural information in scoring systems.

Introduction

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality after surgery.[1] Comprised of deep vein thrombosis and pulmonary embolism, VTE increases the risk of mortality in postoperative patients up to 13 times.[1–4] When VTEs are not fatal, many patients have significant side effects from the physiological response to the emboli and the treatments necessary

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to avoid progression.[5] Prevention of VTE is important for patients and is a quality indicator for postoperative care.

Selecting a perioperative thromboprophylaxis approach requires a physician to balance the risk of VTE and the potential for an increased risk of bleeding. Most studies that report VTE rates fail to report rates of bleeding, preventing informed decision making for thromboprophylaxis ordering.[1,6,7] To help surgeons assess the potential benefits and harms of VTE prophylaxis, data regarding the risk and timing of bleeding events for specific procedures is important.

Guidelines are available to facilitate evidence-based use of thromboprophylaxis after surgery.[8,9] In 2012, the American College of Chest Physicians published a landmark article on thromboprophylaxis after non-orthopedic surgery.[8] This guideline suggested thromboprophylaxis use should be based on risk stratification using the Caprini score.[8] The Caprini score incorporates patient and procedure variables into a risk score. We have previously shown this method is insufficient at completely discriminating VTE risk among patients after major urological surgery for cancer.[10] We reported that almost all urologic cancer patients were categorized as high risk for VTE using the Caprini score, despite having very different absolute risks of VTE. As a result, we suggested that improvements to scoring systems and procedure-specific, VTE prophylaxis strategies were required. Recently, thromboprophylaxis guidelines in urology have been published that are procedure specific and provide recommendations based on the procedure type and patient risk factors.[9] For this study, we hypothesized that all abdominopelvic procedures frequently performed for cancer would be associated with VTE risk, independent of Caprini score.

Methods

The Ottawa Hospital Research Ethics Board approved this study. The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) was queried for patients undergoing major abdominopelvic surgery between 2005 and 2016. Surgical procedures were included if they were major abdominal and pelvic surgeries by general surgery (surgical oncology), thoracic surgery, urology, or gynecology, with at least 10% of patients receiving the procedure for cancer. The frequency of cases performed for cancer was determined by identifying patients with an International Classification of Diseases code for cancer (Appendix 1). We selected a 10% lower limit cutoff of cancer cases to ensure there was an adequate population of patients receiving the operation for oncologic purposes. Abdominal and pelvic surgeries that were usually performed for non-malignant pathology (eg, laparoscopic appendectomy) with <10% of patients with an International Classification of Diseases code for cancer were excluded. Cancer is a major risk factor for VTE, and patients with cancer are commonly prescribed thromboprophylaxis. Once a procedure met the 10% cutoff for malignancy, all cases (cancer and non-cancer) were included in analyses to allow for optimal risk assessment. Operations were identified with Current Procedural Terminology codes. Current Procedural Terminology codes for similar procedures were grouped together to form a total of 28 procedures (Appendix 2). Previous studies using NSQIP data for similar procedures were consulted to ensure the grouping of codes was accurate across surgical specialties and consistent with current literature.[11–15]

Patient and procedural information was extracted from NSQIP, including all variables available that contribute to the Caprini score. Not all Caprini score variables are included in NSQIP, therefore we calculated the minimum Caprini score using the following patient and procedure characteristics, with methods that we have previously reported.[10] Patient characteristics included age (<41, 41–60, 61–74, ≥75 years), body mass index ≥25 kg/m^2 (yes/no), sepsis <1 month (yes/no), serious lung disease <1 month (yes/no), pregnancy or postpartum <1 month (yes/no), acute myocardial infarction <1 month (yes/no), congestive heart failure <1 month (yes/no), bed rest (yes/no), abnormal pulmonary function (yes/no), and malignancy (yes/no). Procedure characteristics included laparoscopic surgery (yes/no) and major surgery >45 minutes (yes/no).

The primary outcome was the risk of VTE (deep vein thrombosis or pulmonary embolism) within 30 days postoperative for each surgical procedure. In NSQIP, a VTE is a blood clot detected on imaging and the initiation of treatment for this within 30 days. Symptomatic and incidentally detected VTEs would be included. A secondary outcome was the risk of red blood cell (RBC) transfusion within 30 days postoperative for each procedure. VTE and RBC transfusions are recorded in NSQIP by trained nurse abstractors. NSQIP data have previously been shown to be highly accurate.[16] Postoperative bleeding was assessed by reporting the proportion of patients receiving an RBC transfusion for each procedure. The timing of VTE and transfusion were also reported. VTE was reported as inpatient (during the index admission) or outpatient (after discharge from the index admission). Timing of transfusion is recorded in NSQIP by the number of days postoperative the transfusion is given.[17] Transfusions on the day of surgery were defined as those received on postoperative day 0. Inpatient transfusions were defined as those received before discharge from hospital. Post-discharge transfusions were those received after discharge from the index admission. The risk of VTE and RBC transfusion by 30 days postoperative were assessed for each procedure and reported to provide readers a better context of the risk-to-benefit assessment when considering thromboprophylaxis.

We sought to explore why current risk stratification methods (eg, Caprini score) may not sufficiently discriminate risk in abdominopelvic surgeries. We hypothesized 1 reason why the current risk stratification is inadequate was the method of inclusion of operative (OR) time in scoring systems. To investigate the effects of OR time on risk of VTE, OR time was divided into 1-hour increments from <1 hour to >10 hours.

A multivariable log binomial regression model was used to determine whether there was an association between individual procedures and VTE, adjusting for Caprini score. The referent surgical procedure was the operation with the lowest risk of VTE. A second multivariable model was used to assess for the association between individual procedures and VTE, adjusting for Caprini score and OR time using 1-hour time intervals. The referent OR time was <1 hour because this was the time with the lowest risk of VTE. The Caprini score suggested by the American College of Chest Physicians' guideline does partially stratify VTE risk using OR time, with a cutoff of 45 minutes. We did not remove the time variable from the Caprini score in these models because the primary purpose of these models was to explore whether the individual procedure risk for VTE was independent of OR time, not to optimize the OR time variable. No adjustment was made for multiple testing for either multivariable analyses. SAS software version 9.4 for Windows was used for analyses (Microsoft, Cary, NC).

Area under the curve (AUC) analyses were performed to assess if adding a surgical procedure to a baseline model including the Caprini score improved the association of the model with VTE events. The AUCs were compared using a Z-test. The category-free net reclassification index (NRI) of the two models was calculated. NRI examines the effect of including a new variable into an established risk-assessment tool on the association.[18,19] In this paper, we compared the association of VTE events between the Caprini score alone (baseline model) and with the addition of surgical procedures.

Results

A total of 896,441 patients underwent 1 of 28 major abdominopelvic operations during the study period (Fig 1). The overall risk

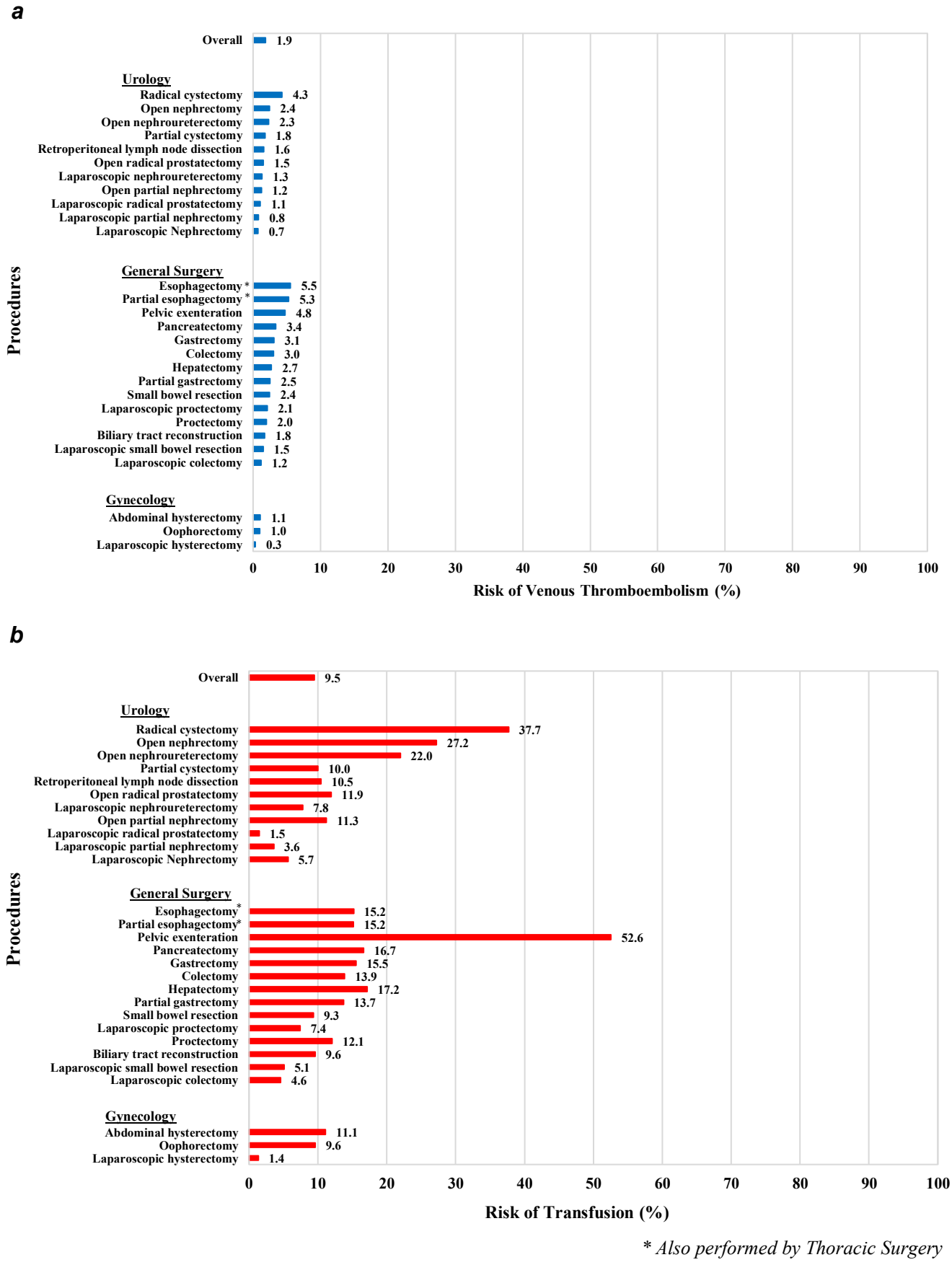


Fig 1. Risk of venous thromboembolism (a) and transfusion (b) for abdominopelvic surgery performed for cancer.

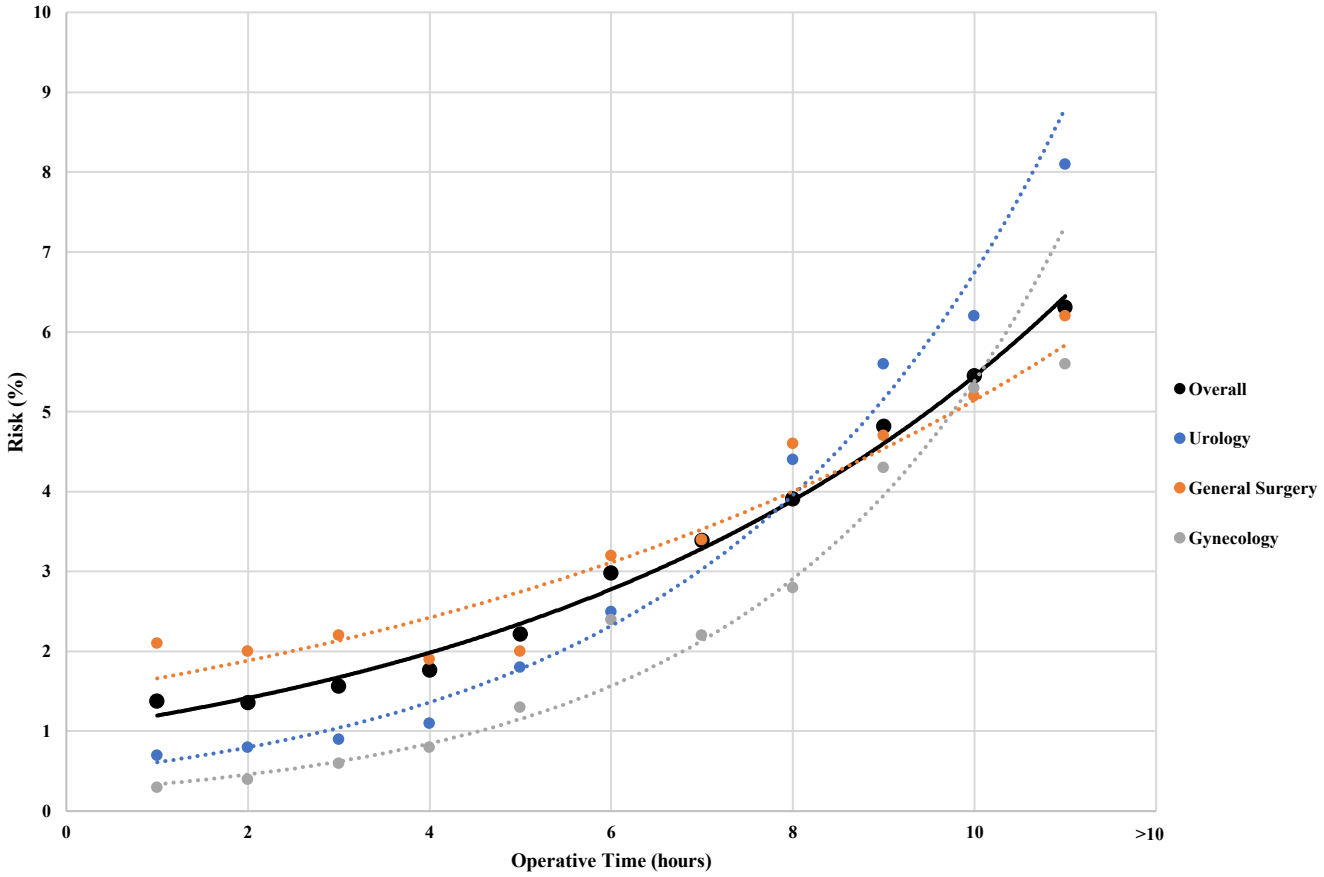


Fig 2. Venous thromboembolism risk by operative time and surgical specialty.

of VTE was 1.9% (n = 16,665) and RBC transfusion was 9.5% (n = 84,889) by 30 days after surgery (Fig 1). The risk of VTE and transfusion by procedure is displayed in Fig 1. The risk of VTE and transfusion were presented together to provide easy reference for physicians to assess the potential net benefit of VTE prophylaxis. Procedures with the highest risk of VTE were esophagectomy (5.5%), partial esophagectomy (5.3%) pelvic exenteration (4.8%), and radical cystectomy (4.3%). The highest risks of RBC transfusions were seen after pelvic exenteration (53.6%), radical cystectomy (37.7%), open nephrectomy (27.2%), and open nephroureterectomy (22.0%).

Using the Caprini score, 61.5% (n = 550,983) of patients were classified as high risk for postoperative VTE, and an additional 34.4% (n = 308,630) were classified as moderate risk. The risk of VTE and transfusion for all high-risk patients was 2.4% and 12.1%, respectively. The risk of VTE was 0.9% for low risk and 1.0% for moderate risk patients on the Caprini score.

Increasing OR time was associated with an increased risk of VTE and RBC transfusion on univariable analyses. The risk of VTE for procedures <1 hour was 1.4%, and RBC transfusion was 6.2%. The risk of VTE increased with each increase in 1 hour of OR time (Fig 2). For example, surgeries lasting 10 hours had a VTE risk of 6% compared with 2% for surgeries lasting 5 hours. When VTE risks were separated by surgical specialty, the increase in risk of VTE by OR time was similar between specialties (Fig 2).

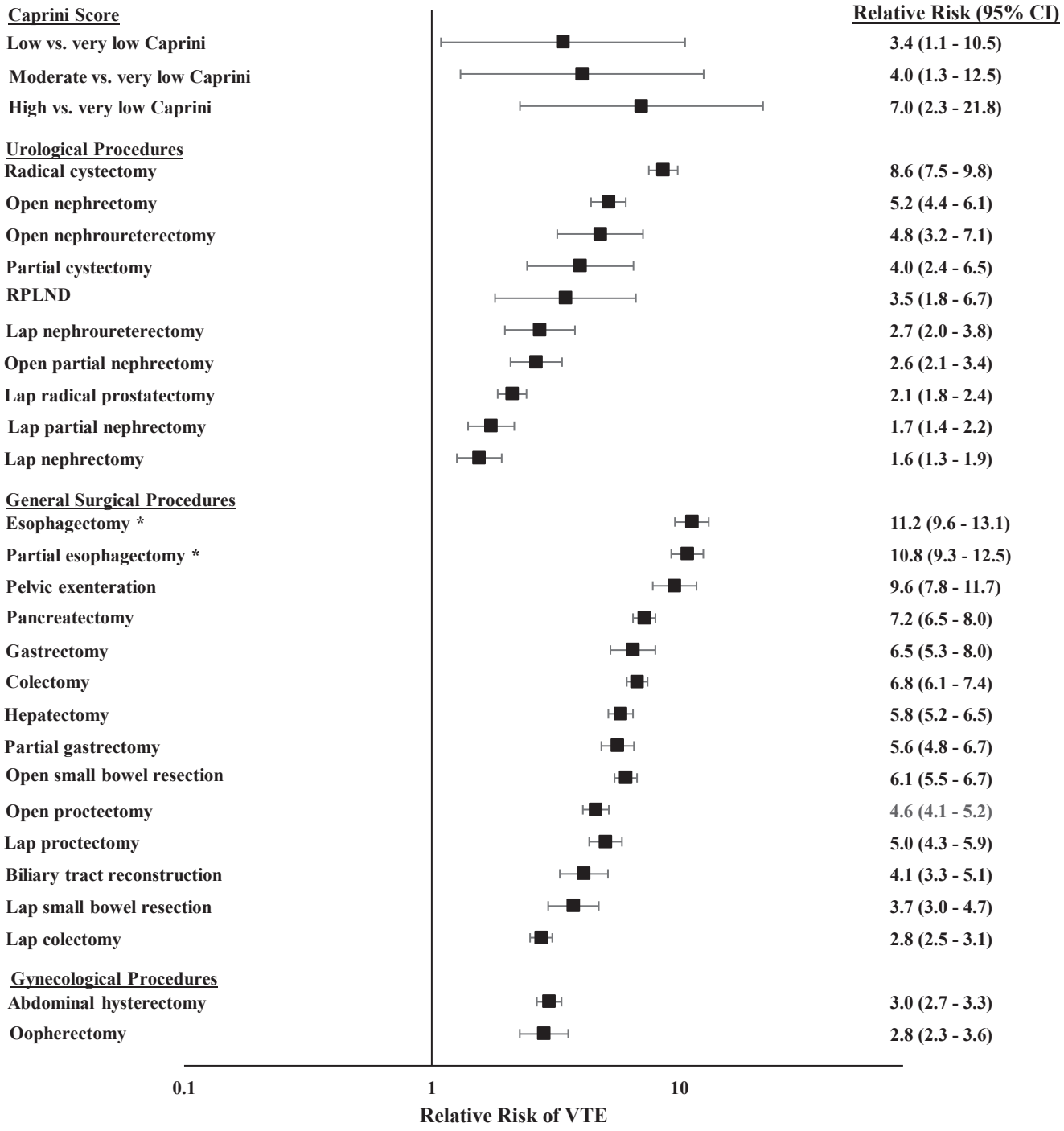
The timing of VTE and transfusion after surgery was assessed because this may affect the timing of VTE prophylaxis. For VTEs, 36% (n = 6,057 of 16,665) occurred after discharge from hospital. For transfusion, almost all occurred during the index admission (99.6%, n = 82,447 of 82,787). Sixty-one percent of transfusions occurred on the day of surgery (n = 50,754) and 17% occurred on postoperative day 1 (n = 14,693). Very few transfusions occurred after hospital discharge (0.4%, n = 340).

Multivariable analyses showed all surgical procedures had an increased risk of VTE compared with the referent operation, despite adjusting for the Caprini score (Fig 3). For example, patients undergoing esophagectomy had a 11.2 times greater risk of VTE than those undergoing laparoscopic hysterectomy (referent procedure), despite adjusting for the Caprini score. The rate of VTE in patients undergoing laparoscopic hysterectomy (referent procedure) was 0.3%. In the second multivariable analysis, where OR time in 1-hour time intervals was included, the relative risk difference narrowed between individual procedures and the referent procedure; however, there remained significant differences in VTE risk (Fig 4). This indicated the addition of 1-hour time intervals to Caprini may improve discrimination but not enough to avoid procedure specific guidelines.

The AUC for the Caprini score alone was 0.59 (baseline model). The second model including the Caprini score (baseline model) and surgical procedure had an AUC of 0.68 ($P < .0001$). The NRI comparing the Caprini score alone to the Caprini score with surgical procedures showed improvement in risk prediction with the inclusion of surgical procedures. The NRI was 0.54 (95% confidence interval 0.52–0.55, $P < .001$), with 44% of events and 10% of non-events being correctly reclassified.

Discussion

VTE is an important and potentially preventable cause of postoperative morbidity and mortality.[1,5] This study characterized the risk of VTE and transfusion for major abdominopelvic surgeries

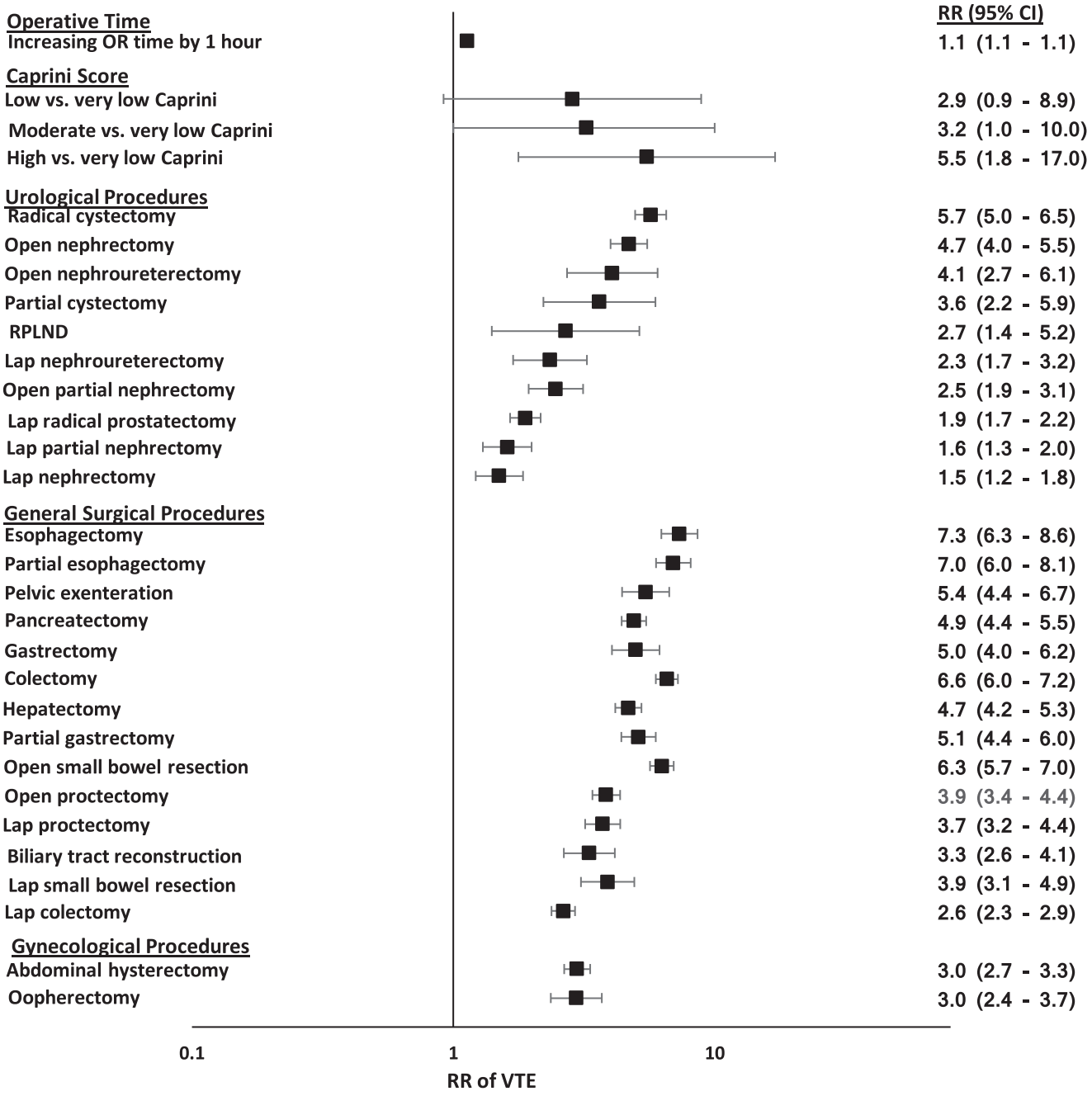


*VTE = venous thromboembolism, vs. =versus, * = also performed by Thoracic Surgery, RPLND = retroperitoneal lymph node dissection, Lap = laparoscopic, CI = confidence interval; Laparoscopic hysterectomy was used as the referent procedure for all procedures*

Fig 3. Adjusted association between Caprini category, surgical procedure, and venous thromboembolism.

frequently performed for cancer. Overall, 1.9% of patients experienced a VTE and 9.5% received a transfusion within 30 days of surgery. This study also confirmed that for patients undergoing major abdominal and pelvic surgery, individual surgical procedures are independent risk factors for VTE, despite adjusting for Caprini score.

Postoperative thromboprophylaxis guidelines are available for patients undergoing major abdominopelvic surgery.[8,9] The most widely accepted guideline suggests calculating patients' Caprini scores to stratify their risk of VTE when deciding on a thromboprophylaxis strategy.[8] While the Caprini score does stratify patients, we have previously shown that this method is insufficient for completely determining risk in urological procedures.[10] In the current study, we extended our analyses to patients undergoing major abdominal or pelvic surgery performed by general surgery, gynecology, and thoracic surgery, and found similar results. This means that although many patients undergoing abdominopelvic



**VTE = venous thromboembolism, RR = relative risk, RPLND = retroperitoneal lymph node dissection, Lap = laparoscopic, OR = operative, vs. = versus, min = minutes, CI = confidence interval*

Fig 4. Adjusted association between operative time, Caprini category, surgical procedure, and venous thromboembolism.

surgery are classified as high risk on the Caprini score, patients in the high-risk category undergoing some procedures are at significantly higher risk for VTE than others and may benefit from different prophylaxis strategies. For example, in our cohort, a patient undergoing an esophagectomy has 11 times the risk of a VTE postoperatively than a patient undergoing a laparoscopic hysterectomy, despite similar risk classification using the Caprini score.

Incorporation of surgical procedures into risk-assessment tools may allow for improved risk stratification for patients undergoing abdominopelvic surgery for cancer. Our results show that when a surgical procedure was included as a variable in models, in addition to the Caprini score, the model's prediction for VTE events improved. This is seen with the improvement in AUC when surgical procedure was included (0.68 vs. 0.59, $P < .001$) and in the NRI. In fact, using the calculated NRI, incorporating surgical procedures into the Caprini score, would increase the true-positive rate by 44% and decrease the false-positive rate by 10% ($P < .001$). There are published concerns regarding the use of NRI independently; however, with the AUC, there is support that risk prediction could be improved.[19,20] These data indicate that risk stratification could be improved by including more granular data about the baseline risk of individual procedures in VTE scoring tools, or by creating a

system that starts by assigning a baseline risk for each procedure that may be modified by patient or additional procedure characteristics, such as in the European Association of Urology VTE guidelines.[9]

There are many factors that differ between surgical procedures, which may explain the differences in VTE risk. We hypothesized that OR time may influence the risk of VTE. OR time is included in several risk stratification scores. For example, in the Caprini score used in thromboprophylaxis guidelines, OR time is categorized as greater or less than 45 minutes.[8,21] We hypothesized that a more detailed breakdown of OR time beyond a 45-minute cutoff may improve risk stratification. Indeed, the inclusion of more detailed OR time categories for risk assessment has been described by Caprini, yet to our knowledge has not been validated or incorporated into clinical guidelines.[8,22] Longer operations are often more complex and may involve more advanced disease or challenging dissection. Figure 2 illustrates that the risk of VTE rises with each additional hour of surgery. We included OR time categorized by hour from less than 1 to greater than 10 in a multivariable analysis with Caprini score and surgical procedure and found that the variability in VTE risk between procedures was diminished, but not negated. This indicates that OR time may account for some of the differences in risk observed between procedures, but there remain other inherent procedure factors affecting VTE risk that remain unaccounted for. Determining these factors and incorporating them into VTE risk assessment tools may allow for more accurate assessment of risk. Future studies should examine how the OR time variable could be improved in available risk stratification models. However, until broadly applicable scoring systems improve, procedure-specific guidelines are needed to properly assess risk.

Venous thromboprophylaxis is effective for preventing VTEs after surgery.[8,23] Patients who receive major abdominopelvic surgery, however, are also at risk of bleeding, with procedures associated with the highest risk of VTE frequently also having a high risk of bleeding.[8,24] Selection of a thromboprophylaxis approach must weigh the benefit of reducing VTEs against the risk of increasing bleeding. Most studies that examine VTE risk in the surgical literature have not reported bleeding risk.[1,6,7] This study provides transfusion risk for all procedures for which VTE risk are reported, as well as timing of VTE and transfusions. We believe these data provide critical context for clinicians to weigh decisions about the net benefit of VTE prophylaxis. Notably, most of the bleeding requiring transfusion occurred within 1 day of surgery (78%) and very few (0.4%) occurred after hospital discharge. The median time to VTE was 9 days postoperative and 36% of all VTEs occurred after hospital discharge. Therefore, most of the bleeding risk is intraoperative or very early in the postoperative period; whereas, VTE risk remains elevated for a longer period of time, including after discharge from hospital. These data may help guide surgeons to weigh the pro and cons of thromboprophylaxis at various time points perioperatively, such as when selecting if extended duration prophylaxis is advisable.

This study has several strengths compared to others in the VTE surgical literature. Most importantly, both VTE and transfusion risk are reported, providing more data to determine the net benefit of VTE prophylaxis for a given patient and procedure. Second, data for a large number of patients undergoing numerous abdominopelvic procedures performed by multiple specialties in multiple institutions are presented, making the study broadly applicable. Finally, we found that the Caprini score, which is recommended in the guidelines to risk stratify patients, may be improved by including more detail about procedures, and possibly OR time.

There are limitations to assessing VTE risk using NSQIP data. Most notably, NSQIP does not include data regarding thromboprophylaxis use. It is likely that patients in NSQIP received variable VTE prophylaxis strategies based on their procedure, physician, medical comorbidities, and institution. Bleeding events that did not require transfusions were not recorded and VTE events that were not symptomatic or detected on imaging were missed. The use of RBC transfusion to assess for postoperative bleeding is a limitation of using NSQIP, given the variability in physician ordering of transfusions. NSQIP also only captures RBC transfusions and not transfusions of other blood products. The risk reported for VTE and bleeding in this study represents a mean for each procedure. Some patients receiving these procedures will have higher or lower risk of VTE and bleeding, which may depend on the VTE prophylaxis strategy used. Despite this limitation, these data have face validity when compared to other studies reporting VTE and bleeding risk for individual procedures and provide a good reference for clinicians who want to develop a strategy to optimize care for their patients. Furthermore, it is likely that patients receiving procedures with higher VTE risk in this study were more likely to receive VTE prophylaxis, which would bias the results against our finding that the individual procedure is an independent risk factor for VTE, thus strengthening our result. A second limitation is not all variables included in the Caprini risk assessment tool are recorded in NSQIP. The minimum Caprini scoring system used in this study may have underestimated the VTE risk of some patients. Of note, most of the patients in this study were classified as high risk using a minimum Caprini score; therefore, it is unlikely this limitation significantly influenced our finding that different surgical procedures have different VTE risk, independent of Caprini. NSQIP does not report cancer stage and grade, which may influence VTE and bleeding risk. Studies are needed to assess the effect of these factors on the risk of VTE and transfusion for individual procedures. Finally, NSQIP only records outcomes to 30 days postoperative. Any VTE or transfusion occurring after that time would not be accounted for in this study. Previous literature has found the majority of VTEs and major bleeding episodes occur within 30 days postoperative, so our study should capture most of the events that occurred in our cohort.[24-26]

In conclusion, VTE is an important cause of postoperative morbidity and mortality after abdominopelvic surgery. Developing the optimal thromboprophylaxis strategy requires knowledge about procedure specific risk of VTE and bleeding, so that clinicians and patients may weigh the net benefit of prophylaxis on a case by case basis.

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Conflict of interest/Disclosure

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Supplementary materials

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