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## Article

# Prevalence and Clinical Burden of Venous Thromboembolic Events (VTEs) in Contemporary Total Knee Arthroplasties (TKAs) in US Hospitals

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**Abstract: Introduction:** Total knee arthroplasty (TKA) is a common orthopedic procedure driven by factors such as an aging population, rising obesity rates, and surgical advancements. Despite improved venous thromboembolism (VTE) prophylaxis, eradication remains challenging, necessitating personalized prevention strategies. This study aims to identify predictors of VTE following TKA. **Methods:** A retrospective analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database (2016-2021) included 367,365 patients who underwent TKA (CPT code 27447). Univariate and multivariate analyses assessed preoperative factors associated with deep vein thrombosis (DVT) and pulmonary embolism (PE). **Results:** Significant associations were found between demographic and clinical variables and VTE prevalence. Notable predictors of DVT included female sex (OR=1.2, p=0.001), younger age (OR=1.2, p=0.001), Hispanic ethnicity (OR=1.2, p=0.026), and chronic obstructive pulmonary disease (COPD) (OR=1.4, p=0.001). Independent functional status was a strong predictor of both DVT (OR=5.0, p=0.001) and PE (OR=0.53, p=0.033). Smoking (OR=0.7, p=0.001), COPD (OR=1.4, p=0.005), congestive heart failure (OR=2.1, p=0.001), and malignancy (OR=2.9, p=0.009) were significant predictors of PE. **Conclusion:** The study underscores the impact of demographic factors (gender, age, race) and comorbidities (COPD, CHF, malignancy) on VTE risk post-TKA. Preoperative mobilization status emerged as a critical indicator of thromboembolic risk. Unexpected findings regarding smoking and PE require further investigation. Overall, the study contributes to optimizing VTE prevention in TKA patients through tailored risk assessment and intervention strategies.

Keywords: Total Knee Arthroplasty; Pulmonary embolism; Deep vein thrombosis; Venous Thromboembolic Event

## Introduction:

Total joint arthroplasties are pivotal procedures in orthopedic surgery, with an annual volume in the United States exceeding 2.8 million. Notably, total knee arthroplasty (TKA) stands out due to their high demand [1]. The growing demand for total knee arthroplasties can be attributed to several factors, including the aging population, rising rates of obesity leading to joint degeneration, and advancements in surgical techniques and implant technology. As the population ages, the prevalence of degenerative joint diseases like osteoarthritis continues to rise, necessitating more joint replacement surgeries [1-3]. Osteoarthritis is a leading cause of joint pain and disability among older adults. Similarly, obesity contributes significantly to joint wear and tear, leading to the need for joint replacement at younger ages than previously observed. Advancements in surgical techniques and implant materials have also played a crucial role in expanding the indications for total knee arthroplasty [1-3]. Total knee arthroplasties will continue to be one of the important major procedures of the United States.

Venous thromboembolism (VTE) can be understood through Virchow's triad, which involves endothelial damage, venous stasis, and hypercoagulability. Orthopedic procedures can iatrogenically induce this triad, making patients more susceptible to VTE [4]. Fortunately, the incidence of VTE

during orthopedic surgeries in the 2010s has significantly decreased to around 1%, thanks to the development of evolving VTE prophylaxis strategies and Enhanced Recovery After Surgery (ERAS) protocols [5-7]. These advancements have played a crucial role in reducing serious patient complications associated with VTE during orthopedic procedures.

Despite advancements in VTE prophylaxis, complete eradication of VTE remains elusive[5-7]. While newer prophylactic measures have reduced VTE risk compared to previous methods, they have not necessarily improved overall survival rates, prompting debates around the need for individualized prophylaxis strategies[8]. Furthermore, studies suggesting that asymptomatic deep vein thromboses (DVTs) may lead to clinical complications in certain patients highlight the potential value of ultrasound screening for DVT in select cases[9]. However, the cost-effectiveness and efficacy of such screening remain uncertain, emphasizing the importance of identifying which patients are at highest risk. The question of who constitutes a high-risk patient is therefore crucial in optimizing VTE prevention strategies and clinical outcomes.

The ability to predict which patients are more susceptible to VTE is pivotal in advancing effective preventative strategies. It is noteworthy that, despite diligent efforts to implement prophylactic measures, instances of VTE may still manifest [5-9]. The scientific community has witnessed a plethora of studies aimed at identifying predictive factors for VTE [5-9]. However, ongoing debates persist surrounding the most efficacious strategies. Our comprehensive study, focusing on predictors of VTE following total knee arthroplasty (TKA), holds distinctive significance as one of the largest in scale, with a case volume exceeding 360,000.

## **Methods:**

### *Study Design:*

To comprehensively assess predictors of postoperative deep vein thrombosis (DVT) and pulmonary embolism (PE) following total knee replacements, a retrospective database analysis was conducted. An anonymized database was meticulously utilized to protect patient data and rights, ensuring no duplication of data across this study.

### *Database*

The analysis was conducted retrospectively using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Participant Use File between 2016 and 2021. This program is a comprehensive initiative that gathers and evaluates preoperative risk factors and postoperative outcomes within 30 days for surgical patients [10]. It provides standardized, risk-adjusted metrics to compare outcomes among hospitals. The data is meticulously collected by dedicated surgical reviewers and undergoes strict auditing protocols to ensure accuracy and consistency. The study focused specifically on patients who had undergone CPT code 27447 procedures, which totaled 367,365 individuals from a cohort of over 5.5 million.

During the thorough univariate analysis, all pertinent preoperative factors were considered. These factors included gender, ethnicity, work relative value unit, diabetes mellitus with oral agents or insulin, current smoker within one year, dyspnea, ventilator dependency, ascites, congestive heart failure within 30 days of surgery, severe COPD history, hypertension requiring medication, preoperative dialysis, disseminated cancer, open wound or wound infection, chronic steroid use, and functional health status prior to surgery. After the univariate analysis, only statistically significant variables were retained for the multivariate analysis.

### *Statistical Analysis*

The categorical variables were carefully presented as numbers and percentages (n, %) and subjected to rigorous analysis using both the Chi-square test and Fisher's exact test, with a predetermined significance level of 0.05. Parameters that exhibited statistical significance underwent additional scrutiny through logistic regression analysis to delve deeper into their predictive value and potential associations with the outcomes of interest.

This comprehensive approach allowed for a robust assessment of the relationships between preoperative factors and postoperative outcomes following CPT code 27447 procedures. The utilization of logistic regression enabled the identification of key predictors while controlling for potential confounding variables, providing valuable insights into the factors influencing patient outcomes in this surgical context. All statistical analyses were meticulously conducted using the Statistical Package for the Social Sciences (SPSS) software, a widely recognized tool for data analysis in medical research.

Results:

The univariate analysis of preoperative variables revealed several significant associations with deep vein thrombosis (DVT) and pulmonary embolism (PE) prevalence among patients undergoing CPT code 27447 procedures. Male gender exhibited a higher prevalence of DVT compared to females (0.73% vs. 0.67%,  $p = 0.001$ ), although there was no significant difference in PE prevalence between genders (0.41% vs. 0.42%,  $p = 0.075$ ). Patients aged 65 years and older demonstrated increased prevalence rates for both DVT (0.71% vs. 0.61%,  $p = 0.001$ ) and PE (0.45% vs. 0.42%,  $p = 0.005$ ) compared to younger patients. Ethnicity was also a significant factor, with Hispanic patients showing a higher prevalence of DVT compared to non-Hispanic patients (0.76% vs. 0.67%,  $p = 0.001$ ). However, ethnicity did not significantly affect PE prevalence in this cohort. Other notable findings include the association between current smoking within one year and decreased PE prevalence (0.30% vs. 0.42%,  $p = 0.017$ ), while dyspnea was significantly associated with higher PE prevalence (1.2% vs. 0.42%,  $p = 0.001$ ). Patients with a history of congestive heart failure (CHF) within 30 days before surgery exhibited higher DVT prevalence (0.71% vs. 0.67%,  $p = 0.733$ ) and higher PE prevalence (0.90% vs. 0.42%,  $p = 0.001$ ). Similarly, those with a history of severe chronic obstructive pulmonary disease (COPD) had significantly higher rates of both DVT (0.88% vs. 0.67%,  $p = 0.003$ ) and PE (0.6% vs. 0.42%,  $p = 0.002$ ). Other factors such as disseminated cancer, functional health status prior to surgery, and open wound/wound infection were also associated with either DVT or PE prevalence. Disseminated cancer was linked to increased PE prevalence (1.2% vs. 0.42%,  $p = 0.014$ ), while lower functional health status prior to surgery was associated with higher rates of both DVT (0.86% vs. 0.67%,  $p = 0.003$ ) and PE (0.73% vs. 0.42%,  $p = 0.018$ ). In summary, these findings underscore the complex interplay of various preoperative factors in influencing thromboembolic risk among patients undergoing total knee replacement surgery. Understanding these associations is crucial for risk stratification and implementing targeted preventive strategies to mitigate the occurrence of DVT and PE in this patient population. The overall prevalence of DVT and PE in the entire cohort was 0.67% (2452 cases) and 0.42% (1580 cases), respectively, providing context for the observed associations within the study population. (Table 1).

Table 1. Preoperative Variables in Univariate Analysis.

Preoperative factors	DVT Prevalence	P-value	PE Prevalence	P-value
Gender (male)	0.73 % (1054)	0.001	0.42 (528)	0.075
Old Patients (above 65-years)	0.71 (1611)	0.001	0.45 (1016)	0.005
Ethnicity (Hispanic)	0.76 % (165)	0.001	0.41 (84)	-
Diabetes mellitus with oral agents or insulin	0.65 % (435)	0.443	0.42 (284)	0.589
Current smoker within one year	0.62 % (172)	0.251	0.30 (84)	0.017
Dyspnea	0.76 % (124)	0.437	1.2 (6)	0.001
Congestive heart failure	0.71 % (17)	0.733	0.9 (21)	0.001
History of Severe COPD	0.88 (106)		0.003	0.6 (72)
Hypertension	0.68 (1579)	0.395	0.41 (972)	0.198



Currently on dialysis (pre-op)	0.67 (4)	0.980	0.34 (2)	0.998
Disseminated cancer	1.0 (5)	0.323	<b>1.2 (6)</b>	<b>0.014</b>
Open wound/wound infection	1.3 (5)	0.228	0.27 (1)	0.599
Steroid use for chronic condition	0.76 (61)	0.156	0.46 (61)	0.566
<b>Functional health status prior to surgery</b>	<b>0.86 (32)</b>	<b>0.003</b>	<b>0.73 (27)</b>	<b>0.018</b>

\* DVT prevalence in all cohort was 0.67% (2452) and PE prevalence in all cohort was 0.42% (1580).

Table 2 presents the predictors of deep vein thrombosis (DVT) in a total knee patient cohort (n=367,365), with both univariate and multivariate analyses revealing significant associations and odds ratios. In the univariate analysis, several factors showed significant relationships with DVT prevalence, including female sex (p=0.001), younger age (p=0.001), Hispanic ethnicity (p=0.001), history of chronic obstructive pulmonary disease (COPD) (p=0.003), and independent functional status (p=0.003). Upon multivariate analysis, these associations were further examined, with female sex (odds ratio=1.2, p=0.001, 95% confidence interval [CI]: 1.092-1.283), younger age (odds ratio=1.2, p=0.001, 95% CI: 1.105-1.307), Hispanic ethnicity (odds ratio=1.2, p=0.026, 95% CI: 1.022-1.406), and COPD (odds ratio=1.4, p=0.001, 95% CI: 1.101-1.608) emerging as significant independent predictors of DVT risk. In addition, independent functional status did maintain statistical significance in the multivariate model (odds ratio=5.0, p=0.001).

**Table 2.** Deep Vein Thrombosis predictors in total knee patient cohort (n=367365).

<i>Univariate</i>	<i>P-value</i>	<i>Multivariate</i>	<i>odds ratio</i>	<i>P-value</i>	<i>Confidence Interval</i>
<b>Female Sex</b>	<b>0.001</b>	<b>1.2</b>	<b>0.001</b>	<b>1.092-1.283</b>	
<b>Young patients*</b>	<b>0.001</b>	<b>1.2</b>	<b>0.001</b>	<b>1.105-1.307</b>	
<b>Hispanic ethnicity</b>	<b>0.001</b>	<b>1.2</b>	<b>0.026</b>	<b>1.022-1.406</b>	
<b>COPD</b>	<b>0.003</b>	<b>1.4</b>	<b>0.001</b>	<b>1.101-1.608</b>	
<b>Functional status</b>	<b>0.002</b>	<b>5.0</b>	<b>0.001</b>	<b>0.072-0.530</b>	

\* under 65 years old.

Table 3 presents the predictors of pulmonary embolism (PE) in a large total knee patient cohort (n=367,365), with univariate and multivariate analyses revealing significant associations and odds ratios. In the univariate analysis, several factors demonstrated significant relationships with PE prevalence, including younger age (p=0.001), independent functional status (p=0.018), history of chronic obstructive pulmonary disease (COPD) (p=0.002), smoking status (p=0.017), congestive heart failure (p=0.001), and metastatic malignancy (p=0.014). Following multivariate analysis, independent functional status (odds ratio=0.53, p=0.033, 95% confidence interval [CI]: 0.304-0.952), smoking (odds ratio=0.7, p=0.001, 95% CI: 0.547-0.855), and COPD (odds ratio=1.4, p=0.005, 95% CI: 1.113-1.826) emerged as significant predictors of PE risk. Additionally, congestive heart failure (odds ratio=2.1, p=0.001, 95% CI: 1.321-3.196) and metastatic malignancy (odds ratio=2.9, p=0.009, 95% CI: 1.301-6.550) were notably associated with higher odds of developing PE in this patient population.

**Table 3.** Pulmonary embolism predictors in total knee patient cohort (n=367365).

<i>Univariate</i>	<i>P-value</i>	<i>Multivariate</i>	<i>odds ratio</i>	<i>P-value</i>	<i>Confidence Interval</i>
<b>Young patients*</b>	<b>0.001</b>		<b>0.76</b>	<b>0.001</b>	<b>0.677-0.848</b>
<b>Independent</b>					
<b>Functional status</b>	<b>0.018</b>		<b>0.53</b>	<b>0.033</b>	<b>0.304-0.952</b>
<b>COPD</b>	<b>0.002</b>		<b>1.4</b>	<b>0.005</b>	<b>1.113-1.826</b>
<b>Smoke</b>	<b>0.017</b>		<b>0.7</b>	<b>0.001</b>	<b>0.547-0.855</b>
<b>Congestive heart failure</b>	<b>0.001</b>		<b>2.1</b>	<b>0.001</b>	<b>1.321-3.196</b>
<b>Metastatic Malignancy</b>	<b>0.014</b>		<b>2.9</b>	<b>0.009</b>	<b>1.301-6.550</b>

\* under 65 years old.

Table 4 illustrates the significance of venous thromboembolisms (VTEs), with corresponding mortality prevalence and prolonged length of stay (LOS) prevalence. The mortality prevalence for DVT was recorded at 0.14% with a P-value of 0.225, while the prevalence of prolonged LOS was 0.32% with a P-value of 0.001. Comparatively, pulmonary embolisms (PE) exhibited a mortality prevalence of 0.78% (P-value = 0.001) and a prolonged LOS prevalence of 0.02% (P-value = 0.001). In general, the overall mortality prevalence was 0.04%, and the prevalence of prolonged LOS was 0.02%.

**Table 4.** importance of VTEs.

<b>VTEs</b>	<b>Mortality Prevalence</b>	<b>P-value</b>	<b>Prolonged LOS Prevalence</b>	<b>P-value</b>
<b>DVT</b>	<b>0.14 (1)</b>	<b>0.225</b>	<b>0.32 (8)</b>	<b>0.001</b>
<b>PE</b>	<b>0.78 (3)</b>	<b>0.001</b>	<b>0.02 (3)</b>	<b>0.001</b>

Mortality Prevalence was 0.04 % and prolonged LOS prevalence was 0.02% in general.

**Discussion**

The study conducted a comprehensive investigation into the predictors and risk factors associated with deep vein thrombosis (DVT) and pulmonary embolism (PE) following total knee arthroplasty (TKA) using data from the National Surgical Quality Improvement Program (NSQIP) Participant Use File (PUF). This analysis aimed to elucidate significant associations and provide insights into the potential contributors to DVT occurrence in this specific patient population.

Thanks to consistent and crucial prophylaxis for venous thromboembolism (VTE), the rates of VTE have markedly decreased from 20 percent in the 1970s to a current rate of 1 percent [11]. This trend is evident based on analyses of the ACS-NSQIP database. Multiple studies focusing on total knee arthroplasty (TKA) up until 2016 have demonstrated a steady decline in deep vein thrombosis (DVT) rates[12,13] Sarpong et al., utilizing the NSQIP database from 2006 to 2016, reported a 30-day DVT rate following TKA of 0.87%, reflecting a decrease from 1.5% between 2006 and 2009 to 0.79% between 2014 and 2016 [12]. Similarly, Warren et al. analyzed data and identified an overall 30-day venous thromboembolism (VTE) rate of 1.4%, including a DVT rate of 0.9% and a pulmonary embolism (PE) rate of 0.6% [13]. The rate decreased from 3.0% (DVT 2.2%, PE 1.0%) in 2008 to 1.4% (DVT 0.9%, PE 0.6%) in 2016, highlighting a significant temporal shift.

Our analysis of the NSQIP database spanning from 2016 to 2021 revealed a VTE rate of 1.09% (0.67% DVT and 0.42% PE), indicating that the declining trend observed from 2006 to 2016 has persisted. Specifically, the DVT rate, previously around 0.9% in studies by Sarpong and Warren, decreased to 0.7%, while the PE rate, previously 0.6%, decreased to 0.4%[12,13] This achievement underscores the advancements made by the orthopedic and arthroplasty communities in effectively managing thromboembolic risks associated with TKA[14,15].

Age gender and race are demographic variables which have widely been shown as influential factors on thrombogenicity of patients[16-25] Gender may be a significant determinant in the risk of developing DVT following TKA[16,17] While some studies suggest that there are no significant differences between genders in DVT incidence post-TKA (18), others have found a higher risk in females compared to males (10). In our study, we found that the female sex is a significant and independent risk factor for DVT. This discrepancy may be attributed to variations in hormonal profiles, clotting factors, and genetic predispositions between genders [19] However, we have found no significant association with PE. Probably it can be explained with idiopathic pulmonary embolism phenomena. In addition, the gender, senesce is also well-known risk factor for thrombosis formation due to aging effects on vascular-endothelial system [20]. In several studies, elderly patients have been shown to be prone to VTEs after TKA [21,22]. We have found that both PE and DVT.

The incidence of venous thrombosis (VTE) varies significantly by race, with individuals of African ancestry exhibiting a substantially higher risk compared to Asian and Hispanic populations, and an intermediate risk for those of European descent [23]. Conversely, Asian populations exhibit lower rates of VTE, which may be due to both clinical under-recognition and genetic factors [23,24] Hispanics, in general, are considered to have an intermediate risk between Asians and whites in terms of VTE risk [24]. Regarding the TKAs, previously, black race has been shown as a risk factor for VTEs [25]. However, in our study, we found that Hispanics have a heightened risk of VTE but not pulmonary embolism (PE).

Cardiopulmonary status is a critical consideration in deep vein thrombosis (DVT) and pulmonary embolism (PE) after total knee arthroplasty (TKA) [18; 26,27]. Our study revealed that patients with preexisting chronic obstructive pulmonary disease (COPD) face a 1.4 times higher risk of DVT, highlighting the impact of cardiopulmonary conditions on thrombotic events post-TKA. Conversely, congestive heart failure (CHF) did not show a significant correlation with DVT in our investigation but was identified as a strong risk factor for PE, aligning with PE pathophysiology [28]. Dyspnea, COPD, and CHF emerged as robust PE predictors in our study, underscoring the importance of a comprehensive preoperative assessment and optimization of cardiopulmonary health to mitigate DVT and PE risks associated with TKA. This emphasizes the need for tailored interventions to address specific cardiopulmonary risk factors in TKA patients.

The impact of preoperative mobilization status on deep vein thrombosis (DVT) outcomes following total knee arthroplasty (TKA) is significant [29-31]. Patients who are partially or fully functionally dependent or require active support face challenges with mobility, leading to prolonged periods of immobilization and increased DVT risk post-TKA [29-31]. Our study revealed that being partially or completely dependent on preoperative mobilization can elevate DVT risk by a factor of 5, emphasizing the need for interventions like physical therapy and early ambulation programs to mitigate this risk among vulnerable TKA patients [32,33]. Furthermore, there is a growing interest in the literature regarding the relationship between patient mobilization and pulmonary embolism (PE) risk [18,34,35]. Our study supported this hypothesis, showing that functionally dependent patients and those needing ventilatory support were predisposed to PE due to challenging mobilization. Our study also contributes novel evidence by demonstrating that preoperative mobilization status can serve as an indicator of PE risk, utilizing a comprehensive database with a substantial patient cohort.

Malignancy has long been recognized as a contributing factor to venous stasis and thromboembolic events [36]. Individuals with a history of malignancy often face an increased risk of postoperative deep vein thrombosis (DVT) and pulmonary embolism (PE), with active malignancies presenting higher rates of complications [37]. Although not consistently recognized as a significant predictor of DVT and PE in total joint arthroplasty studies, our research, aligning with findings from other surgical fields, identifies malignancy as a significant risk factor specifically for PE, though not for DVT.

While it is believed that smoking could theoretically act as a trigger for VTE by reducing oxygen saturation and impairing lung function, creating a pro-thrombotic environment, and activating complement/coagulation pathways, current studies offer substantial insights on this matter [38-41]. Indeed, a meta-analysis in the literature mentioned a slight increase in risk[40], but our study did not

find any association with DVT; surprisingly, we observed an inverse association with PE. These contradictory results compared to existing literature necessitate further validation with more comprehensive and prospective data.

## Conclusion

In conclusion, our study provides valuable insights into the predictors and risk factors associated with deep vein thrombosis (DVT) and pulmonary embolism (PE) following total knee arthroplasty (TKA) using data from the National Surgical Quality Improvement Program (NSQIP) Participant Use File (PUF). We observed a continued decline in VTE rates over time, reflecting advancements in prophylactic measures within the orthopedic community. Our findings highlight the significant influence of demographic factors such as gender, race, and age on thrombotic outcomes post-TKA. Specifically, we identified female sex as an independent risk factor for DVT and noted racial disparities in VTE risk. Cardiopulmonary conditions, including chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF), were associated with heightened risks of DVT and PE, respectively, emphasizing the importance of preoperative assessment and optimization. Furthermore, preoperative mobilization status emerged as a critical predictor of thromboembolic events post-TKA, underscoring the need for tailored interventions to enhance patient mobility. Additionally, our study recognized malignancy as a significant risk factor for PE but not for DVT in this patient population. Finally, our observations regarding smoking and its unexpected inverse association with PE warrant further investigation and validation with comprehensive, prospective studies to enhance our understanding of VTE triggers and preventive strategies in TKA patients.

**Author Contributions:** Conceptualization, H.I.B., MJM., and D.T.; methodology, H.I.B., and D.T.; validation, H.I.B.; data curation D.T. writing—original draft preparation, H.I.B., and M.J.M.; writing—review and editing, H.I.B., and D.T.; supervision, D.T.; All authors have read and agreed to the published version of the manuscript.

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