

RESEARCH ARTICLE

# Determinants of Venous Thromboembolism among Hospitalizations of US Adults: A Multilevel Analysis

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## Abstract

### Background

Venous thromboembolism (VTE) is a significant clinical and public health concern. We evaluated a variety of multilevel factors—demographics, clinical and insurance status, preexisting comorbid conditions, and hospital characteristics—for VTE diagnosis among hospitalizations of US adults.

### Methods

We generated adjusted odds ratios with 95% confidence intervals (CIs) and determined sources of outcome variation by conducting multilevel logistic regression analysis of data from the 2011 Nationwide Inpatient Sample that included 6,710,066 hospitalizations of US adults nested within 1,039 hospitals.

### Results

Among hospitalizations of adults, age, sex, race or ethnicity, total days of hospital stay, status of health insurance, and operating room procedure were important determinants of VTE diagnosis; each of the following preexisting comorbid conditions—acquired immune deficiency syndrome, anemia, arthritis, congestive heart failure, coagulopathy, hypertension, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, pulmonary circulation disorders, renal failure, solid tumor without metastasis, and weight loss—was associated independently with 1.04 (95% CI: 1.02–1.06) to 2.91 (95% CI: 2.81–3.00) times increased likelihood of VTE diagnosis than among hospitalizations of adults without any of these corresponding conditions. The presence of 2 or more of such conditions was associated a 180%–450% increased likelihood of a VTE diagnosis. Hospitalizations of adults who were treated in urban hospitals were associated with a 14%–15% increased likelihood of having a VTE diagnosis than those treated in rural hospitals. Approximately 7.4% of the total variation in VTE diagnosis occurred between hospitals.

## OPEN ACCESS

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**Data Availability Statement:** The authors confirm that some access restrictions apply to the data underlying the findings. The Nationwide Inpatient Sample is a public dataset developed by the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD, USA and is available through the AHRQ Healthcare Cost Utilization Project Central Distributor (HCUP) ([http://www.hcup-us.ahrq.gov/tech\\_assist/centdist.jsp](http://www.hcup-us.ahrq.gov/tech_assist/centdist.jsp)). Due to legal and ethical compliance and procedures for data disclosure and safeguards, researchers must send signed HCUP Data Use Agreements (<http://www.hcup-us.ahrq.gov/>

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## Conclusion

The presence of certain comorbidities and hospital contextual factors is associated with significantly elevated likelihood of VTE diagnosis among hospitalizations of adults. The findings of this study underscore the importance of clinical risk assessment and adherence to evidence-based clinical practice guidelines in preventing VTE, as well as the need to evaluate potential contextual factors that might modify the risk of VTE among hospitalized patients.

## Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious clinical and public health concern [1, 2]. VTE not only imposes a substantial socioeconomic burden on healthcare systems, but also is responsible for numerous debilitating health consequences, including morbidity, mortality, disability, and diminished health-related quality of life among affected individuals [1–3]. In the United States, based on the analyses of hospital discharge data for the years 2009–2010, diagnoses of VTE were recorded in as many as 770,000 hospitalizations of adults annually [4, 5]. Studies also have found that more than 70% of patients who experienced VTE events had VTE identified in a community or outpatient setting, and at least 30% of these outpatients with VTE had been hospitalized during the previous 3 months [6, 7]. While the classic Virchow’s triad describes vascular endothelial damage, stasis of blood flow, and hypercoagulability of blood as the three general components for the pathogenesis of venous thrombosis, advances in research have further identified many specific demographic (e.g., advanced age), biological (e.g., increased levels of prothrombin and fibrinogen), behavioral (e.g., smoking), environmental (e.g., long-distance travel), and health conditions-related risk factors (e.g., surgical and comorbid conditions) that show a simultaneous presence or a sequential interplay of transient and persistent risk factors in the development of VTE [8–10].

As an important health condition that potentially is preventable through implementation of thrombosis risk assessment and evidence-based clinical practice guidelines, VTE is especially a concern for hospitalized patients [11–13]. Previous studies have suggested hospital characteristics (e.g., hospital size, ownership, and teaching status) might influence health outcomes (e.g., short-term mortality and complications) among hospitalized patients [14, 15]. Currently, there is considerable interest among health care providers, researchers, and public health professionals to identify individual- and group-level risk factors for VTE, to discern “compositional effects” (e.g., effects of patient characteristics) and “contextual effects” (e.g., effects of socio-environmental or neighborhood characteristics) and to determine sources of variation (e.g., within group and between group) in VTE risk [11, 16, 17]. Such evidence is essential to identify accurately patients who might benefit from VTE prophylaxis and to inform prevention strategies for optimal care. Therefore, to strengthen the epidemiologic evidence and to fill the knowledge gap in this largely unexplored area of research, we evaluated multilevel determinants, comprising demographics, clinical and insurance status, preexisting comorbid conditions, and hospital characteristics, of VTE diagnosis among hospitalizations of US adults by analyzing data from the 2011 Nationwide Inpatient Sample (NIS).

## Methods

### Ethics Statement

All procedures involving human participants and confidentiality were reviewed and approved by the Research Ethics Review Board of the Agency for Healthcare Research and Quality (AHRQ). Patient records for the NIS were anonymized and de-identified prior to public release for analysis. Analysis of deidentified data from the NIS is exempt from federal regulations for the protection of human research participants.

### Data Source

The NIS is part of the Healthcare Cost and Utilization Project sponsored by the AHRQ [18]. It is the largest all-payer inpatient care public database in the United States, with data on 5–8 million annual unweighted hospitalizations of patients covered by Medicare, Medicaid, or private insurance, and the uninsured from about 1,000 community hospitals. The NIS sampling frame comprises non-federal, short-term, general and specialty hospitals, and long-term acute care facilities. Excluded from the NIS are short-term rehabilitation hospitals, long-term non-acute care hospitals, psychiatric hospitals, and alcoholism or chemical dependency treatment facilities. The NIS is designed to approximate a 20% stratified sample of U.S. community hospitals that include all hospitalizations in the sampled hospitals [18]. The 2011 inpatient core file contained data for 8,023,590 hospitalizations drawn from 1,049 hospitals in participating states that make up 97% of the population in the United States [19]. Details about the sampling methodology are described elsewhere [18]. We restricted our analysis to a sample of hospitalizations for adults 18 years of age and older ( $n = 6,834,910$ ). After further excluding hospitalizations related to pregnancy, childbirth and puerperium and those with missing information for the specific potential determinants we examined (patient age, sex, and total days of hospital stay; insurance status of primary expected payer; and hospital bed size, location and teaching status, and ownership), a total of 6,710,066 hospitalizations of adults nested within 1,039 hospitals were used as the analytical sample.

### Outcome Variable

The NIS provides a maximum of 25 fields of diagnosis based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* for each sampled hospitalization. We determined VTE diagnosis by the presence of *ICD-9-CM* codes 415.1x, 451.1x, 451.2, 451.8x, 451.9, 453.2, 453.4x, 453.8x, and 453.9 in any of the 25 fields of diagnosis.

### Multilevel Determinants of VTE Diagnosis

We assessed the potential determinants of VTE diagnosis at the levels of hospitalization and hospitals. Those variables were selected for inclusion because they are well-known risk factors for VTE or are relevant to VTE prevention.

**Hospitalization level.** We included demographics (i.e., age, sex, and race or ethnicity –10.1% unstated), clinical and insurance status (i.e., total days of hospital stay, insurance status of primary expected payer, and status of operating room procedure), and 29 preexisting comorbid conditions. The AHRQ 29-comorbidity index originally was developed in 1998 by Elixhauser and colleagues for risk adjustment in health outcome research using administrative data [20]. Previous research has demonstrated that the index can predict accurately health outcomes such as mortality for a general population and for hospitalizations of adults with a VTE diagnosis [4]. In the NIS, these 29 comorbidities are considered as coexisting medical conditions that are not related directly to the principal diagnosis or the main reason for admission, and are likely to have existed prior to the hospital stay [21]. Additionally, all *ICD-9-CM* procedure

codes in the NIS are assigned to one of four broad categories of procedures—minor diagnostic, minor therapeutic, major diagnostic, and major therapeutic—according to the AHRQ Procedure Classes [22]. An operating room procedure was defined as having at least one major diagnostic or major therapeutic procedure during hospitalization [23].

**Hospital level.** We assessed the following hospital characteristics bed size (i.e., small, medium, and large), location and teaching status (i.e., rural, urban non-teaching, urban teaching), and ownership (i.e., “government, nonfederal,” “private, non-profit,” and “private, investor-own”) as potential hospital-level determinants. Approximately one-third of the hospitals in a given region, location, and teaching status combination were classified into categories of small, medium, or large bed size by the NIS [19]. Because rural teaching hospitals were rare and accounted for less than 2% of all hospitals, rural status within the category of “location and teaching” was not classified further by teaching status in the NIS [19].

### Statistical Analysis

We calculated the percentage distribution for and rate of VTE diagnosis among hospitalizations of adults by age, sex, race or ethnicity, total days of hospital stay, insurance status of primary expected payer, and operating room procedure. We also estimated the number and percentage distributions of hospitals by bed size, location and teaching status, and ownership. Because the outcome of interest (i.e., VTE diagnosis) was correlated among each group of hospitalizations of adults who were treated within the same hospitals, we applied a multilevel modeling approach to address clustered data in which analytical units (e.g., individual hospitalizations of adults) were nested within other units of interest (e.g., hospitals) [16]. To evaluate the associations between covariates and outcome (fixed effects) and to determine the variation in outcome (i.e., probabilities of VTE diagnosis) between hospitals (random effects) while accounting for clustered data structure, we specified four 2-level logistic regression models with fixed slopes and a random intercept for each model [16]. More specifically, we constructed model 0, an unconditional empty model with no covariate, to divulge the probabilities of VTE diagnosis between hospitals. Model 1 comprised demographic characteristics, clinical and insurance status (i.e., age, sex, race or ethnicity, total days of hospital stay, insurance status of primary expected payer, and operating room procedure) as individual hospitalization level determinants ( $P < 0.05$ ). Model 2 comprised all model 1 determinants and significant preexisting comorbid conditions ( $P < 0.05$ ). Model 3 comprised model 2 determinants and hospital level determinant (i.e., location and teaching status) ( $P < 0.05$ ). We employed a backward elimination procedure of stepwise regression to remove any predictor with the highest  $P \geq 0.05$  for individual  $t$ -test of null hypothesis  $\beta = 0$ . We repeated the same procedure until  $P < 0.05$  for all predictors in models 1–3. The adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were generated to measure the strength of the associations. The intercept variance and intraclass correlation coefficient

$$\begin{aligned}
 \left[ ICC = \frac{\text{Intercept variance}}{\text{Intercept variance} + \text{residual variance}} \right. \\
 \left. = \frac{\sigma^2 (\text{variance between hospitals})}{\sigma^2 (\text{variance between hospitals}) + \sigma^2 (\text{variance within hospitals})} \right]
 \end{aligned}$$

were calculated to assess between- and within-hospitals variation in VTE diagnosis.[24] We performed weighted analyses to present nationally representative percentage estimates (i.e., frequency distribution and rate of VTE) using Complex Samples for Survey Analysis with SPSS 21 (IBM Corp) and STATA 13 (StataCorp LP) to account for the complex sampling design. We conducted

**Table 1. Percentage distribution and rate of VTE diagnosis among hospitalizations of US adults by demographic characteristics, clinical and insurance status, NIS, 2011.**

Demographic characteristics, clinical and insurance status	Sample distribution			Rate of diagnosis of VTE		
	n <sup>a</sup>	% <sup>b</sup>	CI <sup>c</sup>	%	CI	P-Value <sup>d</sup>
<b>Overall</b>	6,710,066	100	–	2.4	2.4–2.5	
<b>Age (years)</b>						<0.001
18–49	2,305,943	34.3	33.5–35.2	1.5	1.4–1.5	
50–79	3,210,405	47.9	47.3–48.4	2.9	2.8–3.0	
≥ 80	1,193,718	17.8	17.3–18.4	3.0	2.9–3.0	
<b>Sex</b>						<0.001
Male	2,708,723	40.4	39.9–40.9	2.9	2.8–2.9	
Female	4,001,343	59.6	59.1–60.1	2.1	2.1–2.2	
<b>Race or ethnicity<sup>e</sup></b>						<0.001
White	4,176,630	62.3	59.7–64.7	2.5	2.4–2.6	
Black	929,079	13.9	12.6–15.3	2.7	2.6–2.9	
Hispanic	641,244	9.6	8.2–11.3	1.7	1.5–1.8	
Other <sup>f</sup>	338,916	5.0	4.4–5.8	1.7	1.6–1.9	
Not stated	624,197	9.2	7.1–11.8	2.5	2.3–2.7	
<b>Total days of hospital stay</b>						<0.001
< 7 days	5,453,256	81.2	80.7–81.7	1.7	1.6–1.7	
≥ 7 days	1,256,810	18.8	18.3–19.3	5.7	5.5–5.8	
<b>Primary expected payer</b>						<0.001
Medicare	3,142,530	46.9	45.9–47.8	2.9	2.8–3.0	
Medicaid	1,003,379	15.0	14.1–15.9	1.6	1.5–1.7	
Private including HMO	1,972,074	29.3	28.3–30.4	2.2	2.1–2.2	
Self-pay or other payers	592,083	8.8	8.2–9.4	2.1	2.0–2.1	
<b>Operating room procedure</b>						<0.001
No procedure of any kind	2,404,657	36.0	34.9–37.1	2.7	2.6–2.8	
Non-operating room procedure <sup>g</sup>	2,328,118	34.6	33.8–35.5	2.3	2.2–2.4	
Operating room procedure <sup>h</sup>	1,977,291	29.4	28.7–30.1	2.2	2.1–2.3	

a. Unweighted sample size.

b. Weighted percentage may not add-up exactly to 100.0%.

c. 95% confidence interval.

d. P-value for Pearson Chi-Square test.

e. May not be nationally representative because not all participating states collect race or ethnicity information.

f. Included “other race/ethnicity,” “Native American,” and “Asian or Pacific Islander.”

g. Had at least one minor diagnostic or minor therapeutic procedure (without any major diagnostic or major therapeutic procedure) during hospitalization.

h. Had at least one major diagnostic or major therapeutic procedure during hospitalization.

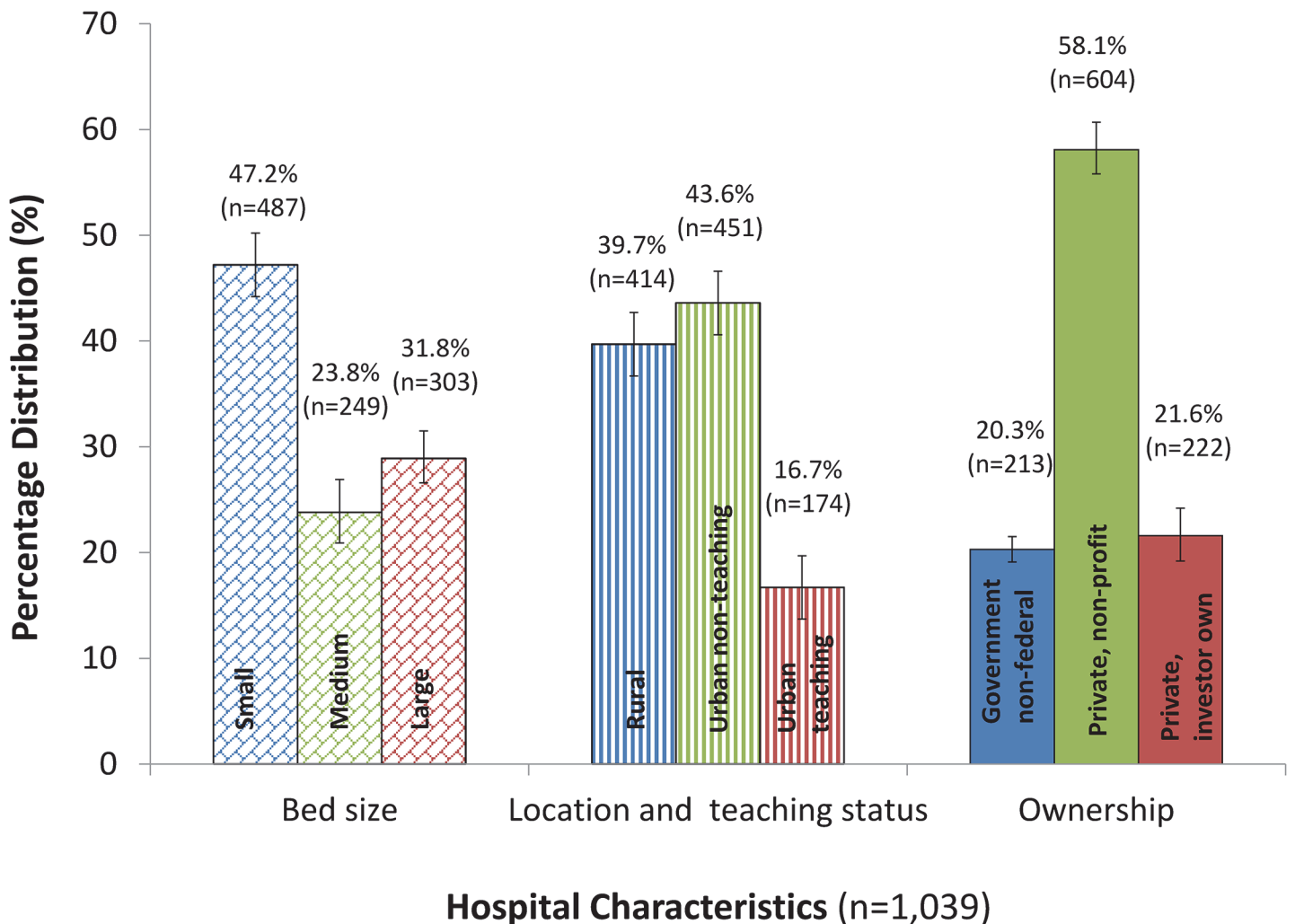
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multilevel modeling using standard procedure for generalized linear mixed models with robust variance estimation [16, 25].

## Results

### Characteristics of Hospitalizations and Hospitals

Table 1 shows that large percentages of all hospitalizations were of adults who were 50–79 years of ages (47.9%), were female (59.6%), were White (62.3%), had less than 7 total days of hospital stay (81.2%), had Medicare as the primary expected payer (46.9%), and had no



**Fig 1. Number and percentage distributions of hospitals (n = 1,039) by hospital characteristics, NIS, 2011.**

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operating room procedures of any kind (36.0%) (Table 1). In 2011, the rate of VTE diagnosis was 2.4% among hospitalizations of adults overall and varied significantly by age, sex, race or ethnicity, total days of hospital stay, insurance status of primary expected payer, and status of operating room procedure ( $P < 0.001$ ). In addition, high rates of VTE diagnosis were observed among subgroups of hospitalizations of adults who were 80 years of age or older (3.0%), were male (2.9%), were Black (2.7%), had at least 7 total days of hospital stay (5.7%), had Medicare insurance as primary expected payer (2.9%), and had no operating room procedures of any kind (2.7%) (Table 1). Large percentages of the 1,039 hospitals in the sample were small bed size (42.2%); urban non-teaching (43.6%); or private, nonprofit (58.1%) (Fig 1).

### Measures of Fixed-Effect Association

The results of fixed-effect association based on three separate regression models are presented in Table 2. When compared with the corresponding subgroups of hospitalizations of adults who were 18–49 years of age, were female, were White, had less than 7 total days of stay, had Medicaid insurance as primary expected payer, or had an operating room procedure,



Table 2. Adjusted odds ratios for VTE diagnosis among hospitalizations of US adults by multilevel determinants, NIS, 2011.

Multilevel determinants <sup>a</sup>	n <sup>e</sup>	VTE diagnosis					
		Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>	
		OR <sup>f</sup>	95% CI <sup>g</sup>	OR	95% CI	OR	95% CI
<b>INDIVIDUAL HOSPITALIZATION LEVEL</b>	6,710,066						
<b>Age (years)</b>							
50–79 (vs 18–49)	3,210,405	1.50	1.45–1.56	1.38	1.34–1.42	1.38	1.34–1.42
≥ 80 (vs 18–49)	1,193,718	1.55	1.51–1.60	1.32	1.27–1.36	1.32	1.27–1.36
<b>Sex</b>							
Male (vs Female)	2,708,723	1.19	1.17–1.20	1.21	1.19–1.23	1.21	1.19–1.23
<b>Race or ethnicity</b>							
Black (vs White)	929,079	1.19	1.17–1.22	1.16	1.14–1.18	1.16	1.13–1.18
Hispanic (vs White)	641,244	0.78	0.75–0.81	0.79	0.77–0.82	0.79	0.77–0.82
Other <sup>h</sup> (vs White)	338,916	0.78	0.74–0.83	0.79	0.74–0.84	0.79	0.74–0.84
Not stated (vs White)	624,197	0.91	0.85–0.98	0.93	0.88–1.00	0.94	0.88–1.00
<b>Total days of hospital stay</b>							
≥ 7 days (vs < 7 days)	1,256,810	3.48	3.38–3.59	3.00	2.91–3.08	3.00	2.91–3.08
<b>Primary expected payer</b>							
Medicare (vs Medicaid)	3,142,530	1.20	1.17–1.24	1.16	1.13–1.20	1.16	1.13–1.20
Private including HMO (vs Medicaid)	1,972,074	1.28	1.23–1.32	1.27	1.23–1.31	1.27	1.23–1.31
Self-pay or other payers (vs Medicaid)	592,083	1.15	1.11–1.20	1.21	1.16–1.26	1.21	1.16–1.26
<b>Operating room procedure</b>							
Non-operating room procedure <sup>i</sup> (vs operating room procedure <sup>i</sup> )	2,328,118	1.02	0.99–1.06	0.97	0.93–1.00	0.97	0.93–1.00
No procedure of any kind (vs operating room procedure)	2,404,657	1.46	1.40–1.53	1.51	1.44–1.57	1.51	1.45–1.57
<b>Acquired immune deficiency syndrome</b>	15,934	– <sup>k</sup>	–	1.33	1.22–1.45	1.33	1.22–1.45
<b>Alcohol abuse</b>	295,743	–	–	0.69	0.66–0.72	0.69	0.66–0.72
<b>Anemia (deficiency)</b>	1,172,235	–	–	1.26	1.24–1.28	1.26	1.24–1.28
<b>Arthritis (rheumatoid)/collagen vascular diseases</b>	179,371	–	–	1.24	1.21–1.28	1.24	1.21–1.28
Chronic blood loss anemia	159,605	–	–	– <sup>g</sup>	–	–	–
<b>Congestive heart failure</b>	564,645	–	–	1.08	1.06–1.10	1.08	1.06–1.10
Chronic pulmonary disease	1,197,654	–	–	–	–	–	–
<b>Coagulopathy</b>	308,968	–	–	1.55	1.51–1.58	1.55	1.51–1.58
Depression	720,809	–	–	–	–	–	–
<b>Diabetes, uncomplicated</b>	1,254,886	–	–	0.85	0.83–0.86	0.85	0.83–0.86
Diabetes with chronic complications	301,405	–	–	–	–	–	–
Drug abuse	270,125	–	–	–	–	–	–
<b>Hypertension (uncomplicated &amp; complicated)</b>	3,280,440	–	–	1.06	1.04–1.08	1.06	1.04–1.07
<b>Hypothyroidism</b>	749,975	–	–	0.96	0.94–0.98	0.96	0.94–0.98
<b>Liver disease</b>	189,225	–	–	0.84	0.81–0.87	0.84	0.81–0.87
<b>Lymphoma</b>	51,298	–	–	1.59	1.51–1.66	1.58	1.51–1.66
Fluid and electrolyte disorders	1,494,353	–	–	–	–	–	–
<b>Metastatic cancer</b>	143,200	–	–	2.91	2.81–3.00	2.91	2.81–3.00
<b>Other neurological disorders</b>	495,916	–	–	1.11	1.09–1.13	1.11	1.09–1.13
<b>Obesity</b>	733,122	–	–	1.39	1.36–1.42	1.39	1.36–1.42
<b>Paralysis</b>	160,997	–	–	1.24	1.20–1.28	1.24	1.20–1.28
<b>Peripheral vascular disorders</b>	393,677	–	–	0.83	0.81–0.85	0.83	0.81–0.85
<b>Psychoses</b>	305,283	–	–	0.97	0.94–1.00	0.97	0.94–1.00
<b>Pulmonary circulation disorders<sup>l</sup></b>	114,931	–	–	2.06	1.98–2.13	2.06	1.98–2.13

(Continued)

Table 2. (Continued)

Multilevel determinants <sup>a</sup>	n <sup>e</sup>	VTE diagnosis					
		Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>	
		OR <sup>f</sup>	95% CI <sup>g</sup>	OR	95% CI	OR	95% CI
<b>Renal failure</b>	786,447	–	–	1.04	1.02–1.06	1.04	1.02–1.06
<b>Solid tumor without metastasis</b>	132,594	–	–	2.23	2.17–2.30	2.23	2.17–2.30
Peptic ulcer disease excluding bleeding	2,140	–	–	–	–	–	–
Valvular disease	237,468	–	–	–	–	–	–
<b>Weight loss</b>	322,748	–	–	1.41	1.38–1.44	1.41	1.38–1.44
<b>HOSPITAL LEVEL</b>							
Bed size							
Medium (vs Small)	1,600,501	–	–	–	–	–	–
Large (vs Small)	4,275,498	–	–	–	–	–	–
<b>Location and teaching status</b>							
Urban non-teaching (vs Rural)	2,843,551	–	–	–	–	1.14	1.07–1.21
Urban teaching (vs Rural)	3,107,244	–	–	–	–	1.15	1.08–1.23
Ownership							
Private, non-profit (vs Gov, non-federal)	5,038,418	–	–	–	–	–	–
Private, investor own (vs Gov, non-federal)	965,283	–	–	–	–	–	–
<b>Variance component</b>	<b>Model 0<sup>m</sup></b>	<b>Model 1</b>		<b>Model 2</b>		<b>Model 3</b>	
<b>Intercept variance</b>	0.261*	0.168*		0.136*		0.133*	
<b>Intraclass correlation coefficient (%)</b>	7.4	4.9		4.0		3.9	

a. Determinants are in bold.

b. Generalized linear mixed model that adjusted for age, sex, race or ethnicity, total days of hospital stay, primary expected payer, and operating room procedure.

c. Generalized linear mixed model that adjusted for all determinants in model 1 and significant preexisting comorbid conditions (i.e., acquired immune deficiency syndrome, alcohol abuse, anemia, arthritis, congestive heart failure, coagulopathy, diabetes, uncomplicated, hypertension, hypothyroidism, liver disease, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, solid tumor without metastasis, and weight loss).

d. Generalized linear mixed model that adjusted for all determinants in model 2 and hospital location and teaching status.

e. Unweighted sample sizes for non-referent subgroups are shown. Referent groups were hospitalizations of adults without corresponding conditions (referent subgroups n = 6,710,066—n for non-referent subgroups).

f. Odds ratio.

g. Confidence interval.

h. Included “other race/ethnicity,” “Native American,” and “Asian or Pacific Islander.”

i. Had at least one minor diagnostic or minor therapeutic procedure (without any major diagnostic or major therapeutic procedure) during hospitalization.

j. Had at least one major diagnostic or major therapeutic procedure during hospitalization.

k. Eliminated variable not in the final model.

l. Hospitalizations with PE and without other diseases in the category were classified as having negative status for the disorder.

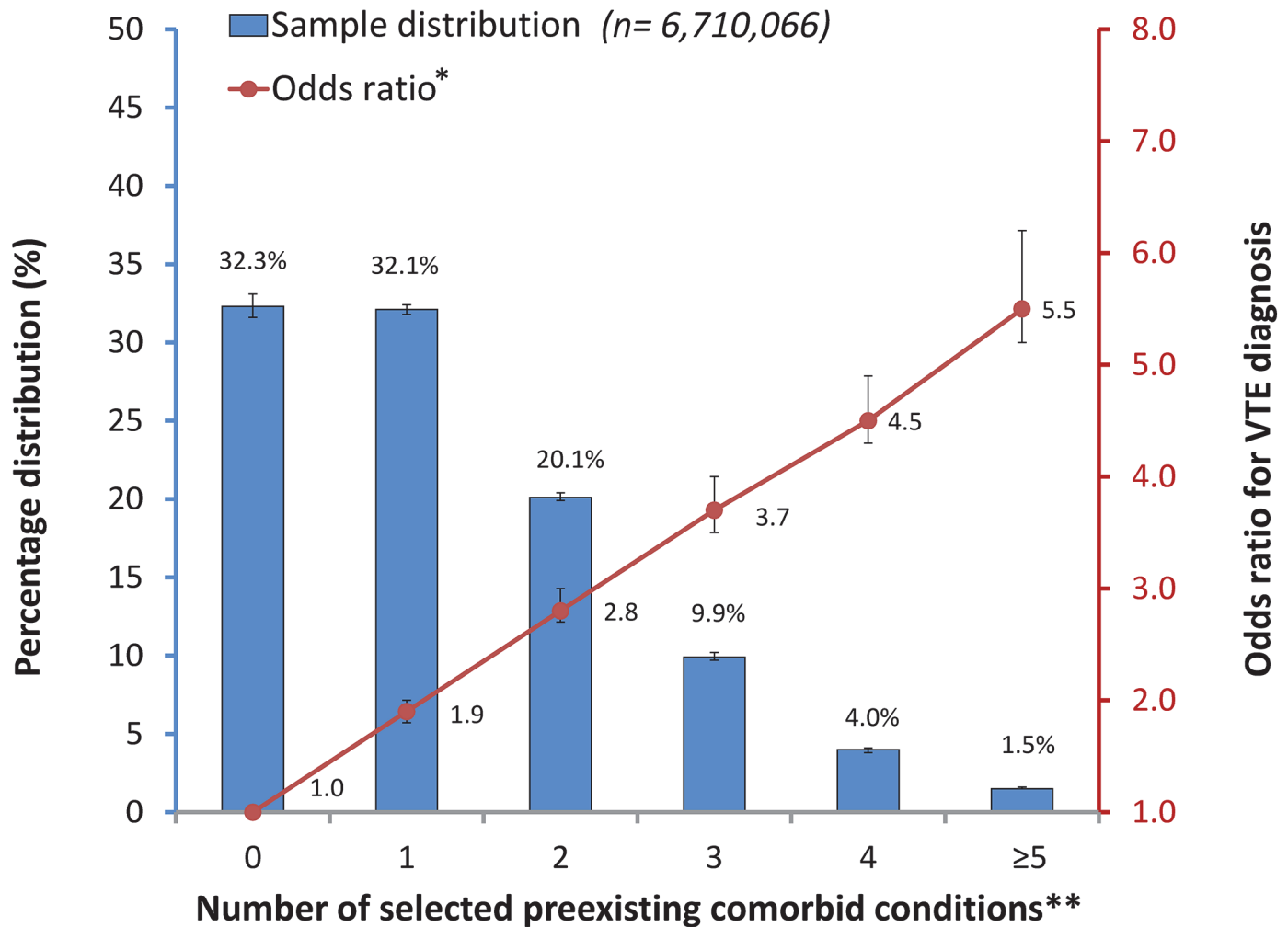
m. Unconditional, empty model with no covariate.

\*P < 0.001.

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subgroups of hospitalizations of adults who were 50–79 years of age (aOR = 1.50; 95% CI: 1.45–1.56), were 80 years of age or older (aOR = 1.55; 95% CI: 1.51–1.60), were male (aOR = 1.19; 95% CI: 1.17–1.20), were Black (aOR = 1.19; 95% CI: 1.17–1.22), had at least 7 total days of hospital stay (aOR = 3.48; 95% CI: 3.38–3.59), had Medicare insurance (aOR = 1.20; 95% CI: 1.17–1.24), had private including HMO insurance (aOR = 1.28; 95% CI: 1.23–1.32), had self-pay or other payers insurance (aOR = 1.15; 95% CI: 1.11–1.20), or had no procedure of any





\*\*Comprised acquired immune deficiency syndrome, anemia (deficiency), arthritis (rheumatoid), congestive heart failure, coagulopathy, hypertension, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, pulmonary circulation disorders, renal failure, solid tumor without metastasis, and weight loss

**Fig 2. Percentage distribution of hospitalizations of US adults and odds ratios for VTE diagnosis by number of selected preexisting comorbid conditions, NIS, 2011.**

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kind (aOR = 1.46; 95% CI: 1.40–1.53) were each positively and independently associated with a VTE diagnosis (model 1). By simultaneously adjusting for the significant preexisting comorbid conditions ( $P < 0.05$ ) and determinants presented in model 1, each subgroup of hospitalizations of adults with acquired immune deficiency syndrome (AIDS), anemia, arthritis, congestive heart failure, coagulopathy, hypertension, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, pulmonary circulation disorders, renal failure, solid tumor without metastasis, or weight loss was associated positively and independently with an increased likelihood (aORs ranged from 1.04 [95% CI: 1.02–1.06] to 2.91 [95% CI: 2.81–3.00]) of VTE diagnosis, compared with those without any of the corresponding 15 preexisting comorbid conditions (model 2). Upon further adjusting for hospital level determinant (i.e., hospital location and teaching status) ( $P < 0.05$ ), hospitalizations of adults who were treated in “urban non-teaching” or “urban teaching” hospitals were associated with 1.14 (95% CI:

1.07–1.21) and 1.15 (95% CI: 1.08–1.23) times increased likelihoods of VTE diagnosis, respectively, when compared with a subgroup of hospitalizations of adults who were treated in rural hospitals (model 3). The patterns and strengths of association of demographic characteristics and clinical and insurance status with VTE diagnosis did not change appreciably in models 2 and 3. Fig 2 illustrates that approximately two of three hospitalizations of adults had at least 1 of the 15 preexisting comorbid conditions that were associated with a VTE diagnosis, and the cumulative number of these diseases corresponded to a 1.9- to 5.5-fold increased likelihood of VTE diagnosis ( $P < 0.001$  for linear trend).

## Measures of Random-Effect Variation

The estimate of intercept variance suggested an appreciable variation in probability of VTE diagnosis occurred between hospitals. The value of ICC indicated that approximately 7.4% of the total variation or differences in probability of VTE diagnosis occurred between hospitals and might have been attributable to potential contextual factors of the hospitals (model 0).

## Discussion

By analyzing a large sample of 6.7 million hospitalizations of adults nested within 1,039 hospitals in the United States from the 2011 NIS, our study expanded existing research through evaluation of both compositional effects from individual hospitalizations and contextual effects from hospitals on VTE diagnosis in the United States. The simultaneous effects of multilevel determinants of VTE encompassing demographic, clinical and insurance status, preexisting comorbid conditions, and hospital characteristics have not been characterized and reported in the past. Our results showed that, of all hospitalizations of US adults, 64.4% had at least 1 and 35.6% had at least 2 of the 15 preexisting comorbid conditions (AIDS, anemia, arthritis, congestive heart failure, coagulopathy, hypertension, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, pulmonary circulation disorders, renal failure, solid tumor without metastasis, and weight loss). When compared with hospitalizations of adults without the corresponding conditions, the presence of these preexisting comorbid conditions showed a 4%–191% increased likelihood of a VTE diagnosis; the presence of 2 or more of such conditions was associated a 190%–450% increased likelihood of a VTE diagnosis. Moreover, approximately a 7.4% variation in VTE diagnosis could have been attributable to contextual factors of hospitals. For example, we found that hospitalizations of adults at urban hospitals had about a 14%–15% increased likelihood of a VTE diagnosis relative to those at rural hospitals, regardless of the hospital's teaching status.

Our findings were consistent with existing evidence showing that factors such as having an advanced age, being male (e.g., for recurrent VTE), being Black, and having had a prolonged hospital stay were associated with an increased risk for VTE [26, 27]. We observed an increased likelihood of a VTE diagnosis when comparing hospitalizations of adults who had no procedure of any kind with those who had an operative room procedure. Despite the greater risk for VTE among surgical patients, previous research showed that medical patients were less likely to receive VTE prophylaxis and had more episodes of VTE and higher rates of pulmonary embolism and death [7, 28–31]. We postulated that hospitalizations of adults with no procedure of any kind included mostly medical patients. Differences in the clinical practice of VTE prophylaxis among clinicians in healthcare settings for patients with various health conditions may affect VTE risk. In addition, some preexisting comorbid conditions (e.g., rheumatoid arthritis, congestive heart failure, pulmonary circulation disorders, obesity, hypertension, and cancer with or without metastasis) have been identified as risk factors for VTE in previous research [32–36]. Diseases or conditions that perhaps had attracted less prominent attention for

their roles in VTE development included iron deficiency anemia, AIDS or human immunodeficiency virus infection, coagulopathy, neurological disorders, paralysis, renal failure, and weight loss [37–44]. In general, the coexistence of two or more conditions can affect other disease or health outcome through the etiological mechanisms of direct causation, associated risk factors, heterogeneity, and independence [45]. The use of our 15 identified preexisting comorbid conditions for VTE risk assessment and prediction might be explored and validated further in future studies.

Hospitals in which people receive care can influence health outcomes via availability and accessibility of health services, as well as prevailing practices and attitudes towards compliance with clinical guidelines and adherence to therapies. The exact reason for an elevated likelihood of VTE diagnosis in hospitalizations at urban hospitals compared with those at rural hospitals was unclear. It could be attributable to the increased availability, accessibility, and utilization of diagnostic services including computed tomography and magnetic resonance imaging, as well as concentration of patients with more complicated conditions. The evidence and effects of significant variation in VTE diagnosis between hospitals were consistent with typical neighborhood effects on health outcomes [46]. Earlier studies have suggested that hospital ownership and teaching status were not associated consistently with patient outcomes even though differences in disease-specific populations may exist [47, 48]. When comparing hospitalizations with Medicaid insurance as the primary expected payer, we observed an increased likelihood of VTE diagnosis among hospitalizations of adults with Medicare; private insurance, including an HMO; or self-pay insurance. Additional research is needed to discern the effect of a higher level structure defined by hospitals or alternative contextual boundaries (e.g., type of insurance payer, team and institutional support, practice, policy, and education) that might shape the environments and processes of healthcare services.

Our results were based on a cross-sectional study which is not designed to establish a cause-effect relationship. The analytical units of the study were hospitalizations and hospitals. The rate of VTE diagnosis among hospitalizations did not necessarily reflect rates per patients, as individual patients could have had multiple hospitalizations. Because the NIS did not identify multiple hospitalizations for individual patients, patient-level of analysis could not be performed. In addition, our study had several other limitations. First, we could not determine if a VTE event had been present on admission or occurred during a hospital stay. Second, 9.2% hospitalizations of adults had missing information on race which might lead to potential misclassification; therefore, caution should be excised when interpreting results related to race. Third, some preexisting comorbid conditions (e.g., obesity and weight loss) were not defined uniformly and measured objectively. The accuracy of *ICD-9-CM* diagnostic codes can be affected by physician documentation; the availability, accessibility, and utilization of diagnostic tests; and reimbursement guidelines [49]. Fourth, the length of hospital stay could be a cause or an effect of having VTE, since patients who develop VTE prior to discharge might also have a longer duration of hospital stay due to the need to treat the VTE. As such, the total days of hospital stay was not necessarily an independent variable for predicting VTE risk in this study. Nevertheless, we did not identify appreciable differences in the associations between having a VTE diagnosis and other covariates upon removing the variable of total days of hospital stay from the regression models. Finally, although we evaluated several hospital characteristics (such as bed size, location and teaching status, and ownership), the variation in VTE diagnosis may have arisen from alternative higher level structures and other contextual factors such as availability and accessibility of advanced equipment and services that were not evaluated [46, 50].

The results from this study have several important clinical and public health implications. To date, a number of evidence-based clinical practice guidelines for VTE prevention using pharmacologic agents and mechanical devices have been developed and are available for

various patient populations [12, 13]. Given that more than two-thirds of hospitalizations of adults might have been associated with one or more preexisting comorbid conditions that might predispose them to a heightened risk for VTE and that the concerns of suboptimal VTE risk assessment and prophylaxis for patients, our findings signify the importance of adherence to VTE prevention guidelines. Health care practitioners need to be informed of various risk factors for VTE risk among hospitalized patients in order to perform appropriate risk assessments to identify and provide counseling to those who might benefit from VTE prophylaxis. Our results also might increase the awareness of VTE among patients and healthcare practitioners and thereby contribute to appropriate decisions for prophylaxis. Patients should keep their doctors informed about their medical history and health conditions, discuss VTE prevention with their doctors during their hospital stay, and adhere to prescribed therapies. Finally, the effects and complexity of multilevel risk factors for VTE illustrate the need for comprehensive public health approaches and evidence-based research to identify multidisciplinary strategies that integrate science, clinical practice, and institutional support to prevent VTE among hospitalized patients.

In summary, the results of our study indicate that the presence of certain comorbidities and hospital contextual factors is associated with significantly elevated likelihood of VTE diagnosis among hospitalizations of adults. The findings of this study underscore the importance of clinical risk assessment and adherence to evidence-based clinical practice guidelines in preventing VTE, as well as the need to evaluate potential contextual factors that might modify the risk of VTE among hospitalized patients.

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## Author Contributions

Conceived and designed the experiments: JT AMG. Performed the experiments: JT AMG MGB SDG HRY LCR. Analyzed the data: JT. Contributed reagents/materials/analysis tools: JT AMG MGB SDG HRY LCR. Wrote the paper: JT. Critical revision of the paper for important intellectual content: JT AMG MGB SDG HRY LCR. Administrative, technical, material support, and study supervision: AMG LCR.

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