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Original Article

Venous thromboembolism and preoperative steroid use: Analysis of the NSQIP database to evaluate risk in surgical patients

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ABSTRACT

Background: Despite several prophylactic strategies, postoperative venous thromboembolism (VTE) remains a major cause of morbidity and mortality. Therefore, the search for modifiable preoperative risk factors is crucial. Few reports have explored this issue but the direct relationship between preoperative steroid use and postoperative VTE in surgical patients remains unexplored.
Methods: We used The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) database in our study. After analyzing patient characteristics, we used multivariate logistic regression to assess the crude and adjusted effect of steroids on VTE, our primary outcome.
Results: Data was obtained for 1,921,901 patients, 58,667 of whom were on glucocorticoids for at least 30 days preoperatively. VTE was higher in patients on steroids with an adjusted odds ratio of 1.54, 95% confidence interval (CI) 1.45–1.64. The adjusted odds ratio for the secondary outcomes: mortality, urinary tract occurrences, wound occurrences, sepsis, cardiac and respiratory adverse events were 1.42 (CI 1.35–1.49), 1.40 (CI 1.30–1.50), 1.58 (CI 1.51–1.66), 1.51 (CI 1.42–1.60), 1.19 (CI 1.11–1.29) and 1.302 (CI 1.301–1.303) respectively.
Conclusions: Our results suggest that surgical patients with prolonged preoperative glucocorticoid intake are at a higher risk of developing postoperative VTE as well as other secondary outcomes including: all-cause mortality, urinary tract occurrences, sepsis, wound occurrences, cardiac and respiratory adverse events. These are important findings since preoperative glucocorticoid use is a modifiable factor.

1. Introduction

Despite early ambulation, use of anticoagulation and other strategies, postoperative venous thromboembolism (VTE) manifesting as deep vein thrombosis (DVT) and pulmonary embolism (PE) remains a major cause of morbidity and mortality in hospitalized patients [1]. Surgical patients are particularly vulnerable to VTE following their procedures, with the risk after major surgeries reaching as high as 20% and PE remaining the leading cause of preventable hospital death in this patient population [2]. Postoperative complications including VTE are a significant burden on patient wellbeing, postoperative recovery and healthcare resources, with previous studies suggesting that VTE prevention could reduce overall healthcare costs by a minimum of $4.5 billion to as much as $39.3 billion annually [3,4]. In light of this heavy toll on patient health and healthcare resources, searching for modifiable preoperative risk factors for postoperative VTE is crucial. Established risk factors for hospital acquired VTE include: surgery, acute medical illness, cancer, trauma, immobilization, central venous catheters, obesity and older age [5]. Prolonged use of glucocorticoids is common for their anti-inflammatory and immunosuppressant effect but is associated with considerable adverse effects that are well documented in the medical literature. Cushing's syndrome has been previously associated with a higher occurrence of VTE [6], while *in vitro* analyses have shown increased levels of procoagulants: clotting factors and fibrinogen with the exogenous use of glucocorticoids [7]. Despite the latter, a rigorous direct analysis of the association between prolonged preoperative glucocorticoid use and postoperative VTE in surgical patients is absent. In this study, we have evaluated whether such a relationship does indeed exist.

2. Methods

2.1. Data collection

The data analyzed was part of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). The participant use file included information from 2008 to 2012. This database is a

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validated outcomes registry including more than 500 hospitals in the United States and worldwide. It was first developed by the veterans' administration and was later adopted by the American College of Surgeons. As mentioned by Khuri in his essay on the establishment of NSQIP, it provides "Reliable data for surgeons, by surgeons" [8].

The database uses trained personnel to collect preoperative, intraoperative and postoperative data using standard definitions. Its main benefit lies in the fact that analysis provides feedback about 30-day risk adjusted mortality and morbidity. [9,10].

2.2. Study design

The database was queried for patients who had undergone all major surgical procedures. In an attempt to minimize confounding and exclude patients with pro-thrombotic tendencies and/or at high risk for postoperative thrombotic complications, we excluded those who had a history of more than one preoperative thrombotic event and those who had preoperative sepsis. Twenty baseline and demographic characteristics were analyzed according to glucocorticoid intake including: sex, age, race, body mass index (BMI), alcohol intake, tobacco consumption, pregnancy, diabetes, operation in the previous 30 days, American Society of Anesthesiologists (ASA) classification, type of anesthesia, surgical specialty, inpatient status, days from admission to operation, perioperative transfusion, infected surgical wound class mean operative time, and emergency cases. System specific variables were also analyzed and included cardiovascular, respiratory, hepatobiliary, renal, hematologic and neurologic parameters.

Glucocorticoid intake was defined according to the ACS-NSQIP user guide. It included patients who required regular administration of oral or parenteral glucocorticoid medications within 30 days prior to the principal operative procedure or at the time the patient is being considered as a candidate for surgery, for a chronic medical condition. It excludes a one-time pulse, or a taper of less than 10 days. Short courses of 10 days or less are also excluded.

Outcomes were also defined according to the ACS-NSQIP user guide. The primary outcome, venous thromboembolism (VTE) was a composite of two outcomes, deep venous thrombosis (DVT) and pulmonary embolism (PE). DVT was defined as the identification of a new blood clot or thrombus within the venous system, which may be coupled with inflammation. The diagnosis is usually confirmed by imaging using duplex, venogram or CT scan. Pulmonary embolism was defined as the lodging of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. Diagnosis usually relies on a high probability V-Q scan, a positive CT exam, Transesophageal echocardiogram, pulmonary arteriogram, CT angiogram or other imaging modalities. Other studied outcomes included mortality, cardiac occurrences (acute myocardial infarction or cardiac arrest necessitating cardiopulmonary resuscitation), respiratory occurrences (pneumonia,

Table 1
Baseline characteristics of patients.

		All (%) N = 1,921,901	No glucocorticoids n (%) N = 1,863,234	Glucocorticoid intake n (%) N = 58,667
Sex	Male	819,129 (42.62)	793,292 (42.57)	25,837 (44.04)
	Female	1,102,772 (57.38)	1,069,942 (57.42)	32,830 (56.00)
Age (years)	(Mean, SD)	56.16 ± (16.90)	56.05 ± (16.90)	59.54 ± (16.40)
	<50	658,517 (34.26)	643,259 (34.52)	15,258 (26.00)
	50–65	614,956 (31.99)	596,230 (31.99)	18,726 (31.91)
	65–80	484,589 (25.21)	466,369 (25.03)	18,220 (31.06)
	>80	163,839 (8.52)	157,376 (8.44)	6463 (11.01)
Race	White	1,461,585 (76.05)	1,415,819 (75.98)	45,766 (78.01)
	Black	184,572 (9.60)	178,423 (9.57)	6149 (10.48)
	Other	275,744 (14.35)	268,992 (14.44)	6752 (11.51)
BMI (kg/cm^2)	(Mean, SD)	29.99 ± 8.09	30.04 ± 8.09	28.5 ± 7.67
	<30	1,131,040 (58.85)	1,092,600 (58.64)	38,440 (65.52)
	>30	790,861 (41.15)	770,634 (41.36)	20,227 (34.48)
Functional status	Independent	1,827,110 (95.33)	1,775,575 (95.30)	51,535 (87.84)
	Partially dependent	68,143 (3.56)	63,037 (3.38)	5106 (8.70)
	Dependent	21,271 (1.11)	19,467 (1.04)	1804 (3.07)
0ASA class	I–II	1,062,394 (55.47)	1,047,067 (56.19)	15,327 (26.13)
	III	727,897 (38.01)	694,506 (37.27)	33,391 (56.92)
	IV–V	124,813 (6.52)	115,052 (6.17)	9761 (16.64)
Type of anesthesia	General	1,742,279 (90.65)	1,688,936 (90.64)	53,343 (90.92)
	Other	179,622 (9.35)	174,298 (9.35)	5324 (9.07)
Surgical subspecialty	General	1,151,504 (59.92)	1,116,201 (59.91)	35,303 (60.17)
	Gynecology	100,073 (5.21)	98,889 (5.31)	1184 (2.02)
	Neurosurgery	59,110 (3.08)	55,487 (2.98)	3623 (6.17)
	Orthopedic	229,604 (11.95)	223,029 (11.97)	6575 (11.21)
	ENT	42,671 (2.22)	41,863 (2.25)	41,863 (71.36)
	Plastic	39,137 (2.04)	38,425 (2.06)	712 (1.21)
	Thoracic	19,637 (1.02)	18,548 (0.99)	1089 (1.85)
	Urology	77,239 (4.02)	75,515 (4.05)	1724 (2.93)
	Vascular	188,182 (9.79)	180,991 (9.71)	7191 (12.25)
	Cardiac	14,664 (0.76)	14,211 (0.76)	453 (0.77)
Days from admission to operation	0	173,065 (9.01)	161,116 (8.64)	11,949 (20.36)
	1	117,102 (6.09)	112,263 (6.02)	4839 (8.24)
	>1	1,631,504 (84.90)	1,589,632 (85.31)	41,872 (71.37)
Mean total operation time (min)		110.50 ± 92.31	110.03 ± 92.13	125.63 ± 96.51
Perioperative transfusion[6]		17,410 (0.91)	15,883 (0.85)	1527 (2.60)
Infected surgical wound class		107,533 (5.60)	101,053 (5.42)	6480 (11.04)
Emergency case		214,198 (11.15)	205,561 (11.03)	8637 (14.72)
Inpatient status		1,228,352 (63.91)	1,181,278 (63.40)	47,074 (80.24)
Alcohol intake in previous 2 weeks[8]		35,206 (1.83)	34,423 (1.84)	783 (1.33)
Tobacco use in past year		370,133 (19.26)	360,283 (19.34)	9850 (16.79)
Pregnancy		2965 (0.15)	2926 (0.16)	39 (0.07)
Diabetes on oral drugs or insulin		289,259 (15.05)	277,245 (14.88)	12,014 (20.5)
Systemic sepsis in previous 48 h		126,346 (6.57)	118,451 (6.36)	7895 (13.45)
Operation within previous 30 days		34,016 (1.77)	31,949 (1.71)	2067 (3.52)

ventilator support for more than 48 hours, or unplanned intubation), wound occurrences (deep incisional surgical site infection or wound dehiscence), urinary tract occurrences (progressive renal insufficiency or acute renal failure) and sepsis (sepsis or septic shock).

2.3. Statistical analysis

We analyzed preoperative and perioperative variables between patients taking glucocorticoids and patients who were not on glucocorticoids, using X^2 for categorical variables and independent sample t-test for continuous variables. Data is presented as numbers and percentages. Statistical significance was assumed with a P value of less than .05.

We also analyzed system specific complications using the same methods in patients who were on glucocorticoids and those who were not.

The unadjusted odds ratio and the 95% were calculated for our primary outcome VTE, and for our secondary outcomes 30-day mortality, cardiac occurrences, respiratory occurrences, urinary occurrences, wound occurrences and sepsis. Then we created multivariate logistic regression models and confounders of clinical significance were adjusted for.

Data was near complete and analyses were performed using SAS (Statistical analysis software).

3. Results

Data were analyzed for 1,921,901 patients who had undergone major surgical procedures from 2008 to 2012. Patients had a mean age of 56.16 (±16.9) years, 819,129 (42.62%) were males and 1,102,772 (57.38%) were females. Of the total sample, 34,016 (1.77%) patients had undergone a major surgical procedure in the past 30 days, and 21,271 (1.11%) had a dependent functional status and required total assistance for activities of daily living. Most common comorbidities included diabetes (15.05%) and dyspnea at rest or upon moderate exertion (8.85%) glucocorticoid intake was present in 58,667 (3.05%) of patients. Table 1 depicts the demographic, preoperative and perioperative characteristics of patients depending on glucocorticoid intake. Table 2 details system-specific morbidities in relation to glucocorticoid intake. Patients on glucocorticoids were more likely to be females, white, with a BMI < 30 and with an independent functional status.

The occurrence of VTE in the studied sample was 0.82%. Glucocorticoid intake was found to be associated with an increased risk of postoperative thromboembolism. From the pool of patients who were on glucocorticoids, 2.1% had postoperative venous thromboembolism while 0.7% of those who were not on glucocorticoids had a postoperative VTE. This outcome was associated with a crude odds ratio (OR) of 2.74 (95% Confidence interval 2.59–2.91, P < 0.0001) for patients on glucocorticoids compared to those who were not. Upon adjustment for clinically relevant variables, we obtained an adjusted odds (AOR) ratio of 1.54 (95% CI 1.45–1.64, P < 0.0001). Table 3 shows the stratification of VTE and glucocorticoid intake in relation to various risk factors. Amongst affected patients on glucocorticoids there appears to be a similar gender distribution, a higher percentage above 50 years of age, a higher percentage of patients that haven't used alcohol in the past 2 weeks nor tobacco in the past year, a bigger portion that hasn't undergone a major surgical procedure in the previous 30 days. Table 4 depicts other studied outcomes including: 30 day mortality, cardiac, respiratory, wound occurrences and sepsis. Mortality in patients on glucocorticoids was 4.3% compared to 1.2% in those who were not on glucocorticoids, with a crude odds ratio of 3.78 (95% CI 3.63–3.94, P < 0.0001). Cardiac occurrences were 1.4% in patients on glucocorticoids, and 0.6% in those who were not, with a crude odds ratio of 2.33 (95% CI 2.18–2.50, P < 0.0001). Respiratory occurrences reached 6.9% in patients on glucocorticoids and 2.3% in those who were not, with a crude odds ratio of 3.08 (95% CI 2.98–3.18, P < 0.0001). Wound occurrences happened in 3.6% of patients on glucocorticoids as opposed to 1.5% of patients who were not on glucocorticoids, and the crude odds ratio was 2.37 (95% CI 2.26–2.47, P < 0.0001). Finally sepsis was found to be prevalent in 2.5% of patients who were on glucocorticoids and in 0.7% of patients who were not on glucocorticoids, with a crude odds ratio of 3.69 (95% CI 3.49–3.89, P < 0.0001). Upon adjustment for clinically relevant variables, 30 day mortality had an AOR of 1.42 (95% CI 1.35–1.49 P < 0.0001), cardiac occurrences had an AOR of 1.19 (95% CI 1.11–1.29, P < 0.0001), respiratory occurrence had an AOR of 1.302 (95% CI 1.301–1.303, P < 0.0001), wound occurrences had an AOR of 1.58 (95% CI 1.51–1.66, P < 0.0001) and sepsis had an AOR of 1.51 (95% CI 1.42–1.60, P < 0.0001).

Table 2
System-specific patient variables.

Variables		All (%) N = 1,921,901	No glucocorticoids n (%) N = 1,863,234	Glucocorticoid intake n (%) N = 58,667
Cardiovascular variables	Dyspnea at rest or with moderate exertion	170,098 (8.85)	159,526 (8.56)	10,572 (18.02)
	Congestive heart failure in previous 30 days	16,019 (0.83)	14,754 (0.79)	1265 (2.16)
	Myocardial infarction in previous 6 months	9129 (0.47)	8598 (0.46)	531 (0.90)
	Previous cardiac surgery	71,377 (0.04)	67,948 (3.64)	3429 (5.84)
	History of peripheral vascular disease	49,378 (2.57)	47,063 (2.52)	2315 (3.94)
Respiratory variables	Current pneumonia	6376 (0.33)	5559 (0.29)	817 (1.39)
	History of severe COPD	90,305 (4.70)	81,726 (4.38)	8579 (14.62)
	Ventilator-dependent in last 48 h	12,353 (0.64)	11,083 (0.59)	1270 (2.16)
Hepatobiliary variables	Ascites in previous 30 days	11,316 (0.59)	10,470 (0.56)	846 (1.44)
	Esophageal varices in previous 6 months	1315 (0.07)	1233 (0.06)	82 (0.14)
Renal variables	Acute renal failure	8995 (0.47)	8208 (0.44)	787 (1.34)
	Presently on dialysis	30,850 (1.61)	28,339 (1.52)	2511 (4.28)
Neurological variables	Hemiplegia	11,595 (0.60)	10,996 (0.59)	599 (1.02)
	Paraplegia	6455 (0.34)	6062 (0.32)	393 (0.67)
	Quadriplegia	1727 (0.09)	1626 (0.09)	101 (0.17)
	Coma lasting > 48 h	776 (0.04)	715 (0.04)	61 (0.10)
	History of transient ischemic attacks	37,152 (1.93)	35,643 (1.91)	1509 (2.57)
	History of CVA with neurological deficit	28,822 (1.50)	27,550 (1.47)	1272 (2.17)
	History of CVA[4] without neurological deficit	26,144 (1.36)	24,923 (1.33)	1221 (2.08)
	Tumor involving CNS	4658 (0.24)	3754 (0.20)	904 (1.54)
Hemato-oncological variables	Bleeding disorder	96,857 (5.04)	89,982 (4.83)	6875 (11.71)
	Weight loss > 10% in previous 6 months	32,035 (1.67)	29,439 (1.58)	2596 (4.42)
	Disseminated cancer	36,798 (1.91)	33,894 (1.82)	2904 (4.94)
	Chemotherapy in previous 30 days	17,685 (0.92)	16,127 (0.86)	1558 (2.65)
	Radiotherapy in previous 90 days	8867 (0.46)	8308 (0.44)	559 (0.95)

Table 3
VTE stratified by patient variables.

		Glucocorticoid intake n (%) N = 58,667	No glucocorticoids n (%) N = 1,863,234	OR_{crude}	CI	p-Value	ORadj1	CI	p-Value
Venous thromboembolic (VTE) event	1241 (2.11)	14,544 (0.78)	2.74	2.59–2.91	<.0001	1.54	1.45–1.64	<.0001	
Stratified by									
Sex	Male	621 (1.06)	7141 (0.38)	2.71	2.49–2.94	<.0001	1.6	1.47–1.74	<.0001
	Female	620 (1.06)	7403 (0.39)	2.76	2.54–3.00	<.0001	1.48	1.36–1.62	<.0001
Age (years)	<50	250 (0.42)	2462 (0.13)	4.33	3.80–4.94	<.0001	1.92	1.67–2.21	<.0001
	50–65	390 (0.66)	4467 (0.24)	2.81	2.53–3.12	<.0001	1.6	1.43–1.78	<.0001
	65–80	441 (0.75)	5298 (0.28)	2.15	1.95–2.38	<.0001	1.39	1.26–1.54	<.0001
	>80	160 (0.27)	2317 (0.12)	1.69	1.44–1.99	<.0001	1.32	1.12–1.56	0.0009
Race	White	990 (1.69)	11,258 (0.60)	2.75	2.58–2.94	<.0001	1.55	1.45–1.66	<.0001
	Black	131 (0.22)	1734 (0.09)	2.21	1.85–2.65	<.0001	1.44	1.20–1.74	0.0001
	Other	120 (0.20)	1552 (0.08)	3.11	2.58–3.76	<.0001	1.57	1.29–1.91	<.0001
BMI (kg/m^2)	<30	803 (1.37)	8133 (0.44)	2.84	2.64–3.06	<.0001	1.56	1.45–1.69	<.0001
	≥30	438 (0.75)	6411 (0.34)	2.63	2.39–2.90	<.0001	1.49	1.34–1.65	<.0001
Alcohol intake in previous 2 weeks	Yes	13 (0.02)	326 (0.02)	1.76	1.003–3.08	0.04	1	0.56–1.79	0.006
	No	1228 (2.09)	14,218 (0.76)	2.76	2.60–2.93	<.0001	1.55	1.46–1.65	<.0001
Tobacco use in past year	Yes	198 (0.34)	2564 (0.14)	2.86	2.47–3.31	<.0001	1.55	1.33–1.80	<.0001
	No	1043 (1.77)	11,980 (0.64)	2.71	2.54–2.89	<.0001	1.55	1.45–1.65	<.0001
Diabetic on oral drugs or insulin	Yes	259 (0.44)	2766 (0.15)	2.18	1.92–2.48	<.0001	1.46	1.27–1.67	<.0001
	No	982 (1.67)	11,778 (0.63)	2.87	2.69–3.06	<.0001	1.56	1.46–1.57	<.0001
Operation within previous 30 days	Yes	92 (0.15)	800 (0.04)	1.81	1.45–2.26	<.0001	1.3	1.04–1.64	0.02
	No	1149 (1.95)	13,744 (0.73)	2.74	2.57–2.91	<.0001	1.56	1.47–1.66	<.0001
Functional status	Independent	975 (1.66)	12,330 (0.66)	2.75	2.58–2.94	<.0001	1.66	1.55—1.78	<.0001
	Partially dependent	169 (0.29)	1383 (0.07)	1.52	1.29–1.79	<.0001	1.17	0.99–1.39	0.05
	Dependent	92 (0.16)	796 (0.04)	1.26	1.01–1.57	0.04	1.12	0.89–1.40	0.32
ASA class [2,3]	I–II	197 (0.33)	4281 (0.23)	3.15	2.73–3.63	<.0001	2.18	1.88–2.52	<.0001
	III	659 (1.12)	7393 (0.39)	1.87	1.72–2.02	<.0001	1.537	1.534–1.539	<.0001
	IV–V	385 (0.65)	28,700 (1.54)	1.6	1.44–1.78	<.0001	1.31	1.17–1.46	<.0001
Type of anesthesia	General	1181 (2.01)	13,591 (0.73)	2.79	2.62–2.96	<.0001	1.54	1.45–1.64	<.0001
	Other	60 (0.10)	953 (0.05)	2.07	1.59–2.69	<.0001	1.64	1.63–1.65	<.0001
Surgical subspecialty	General	794 (1.35)	8177 (0.44)	3.11	2.89–3.35	<.0001	1.61	1.49–1.73	<.0001
	Gynecology	8 (0.01)	437 (0.02)	1.53	0.75–3.09	0.22	0.92	0.45–1.88	0.82
	Neurosurgery	125 (0.21)	740 (0.04)	2.64	2.18–3.20	<.0001	1.68	1.36–2.07	<.0001
	Orthopedic	107 (0.18)	2008 (0.11)	1.82	1.49–2.21	<.0001	1.36	1.11–1.66	0.002
	ENT	8 (0.01)	93 (0.01)	4.49	2.17–9.27	<.0001	2.22	2.20–2.25	<.0001
	Plastic	9 (0.01)	127 (0.01)	3.86	1.95–7.62	<.0001	2.1	0.99–4.44	0.05
	Thoracic	28 (0.05)	327 (0.02)	1.47	0.99–2.17	0.051	1.14	0.76–1.71	0.52
	Urology	22 (0.04)	547 (0.03)	1.77	1.15–2.72	0.0081	1.57	1.01–2.45	0.04
	Vascular	127 (0.22)	1799 (0.10)	1.79	1.49–2.14	<.0001	1.47	1.22–1.78	<.0001
	Cardiac	11 (0.02)	289 (0.01)	1.19	0.65–2.20	0.55	1.02	0.54–1.90	0.94
Inpatient status	Yes	1195 (2.04)	13,393 (0.72)	2.27	2.13–2.41	<.0001	1.53	1.44–1.63	<.0001
	No	46 (0.08)	1151 (0.06)	2.35	1.75–3.16	<.0001	1.73	1.28–2.34	0.0004
Days from admission to operation	0	618 (1.05)	9243 (0.50)	2.56	2.35–2.78	<.0001	1.64	1.50–1.78	<.0001
	1	146	1506	2.28	1.92–2.71	<.0001	1.46	1.22–1.75	<.0001
	>1	477	3791	1.72	1.56–1.90	<.0001	1.4	1.26–1.54	<.0001
Emergency case	Yes	365	3015	2.96	2.65–3.31	<.0001	1.37	1.22–1.54	<.0001
	No	876 (0.01)	11,529	2.54	2.37–2.72	<.0001	1.62	1.51–1.74	<.0001
Perioperative transfusion[6]	Yes	73	549	1.4	1.09–1.80	0.007	1.23	0.95–1.60	0.10
	No	1168 (0.02)	13,995	2.73	2.57–2.90	<.0001	1.56	1.47–1.66	<.0001
Infected surgical wound class	Yes	265	1856	2.27	1.99–2.59	<.0001	1.39	1.22–1.60	<.0001
	No	976	12,688	2.62	2.46–2.80	<.0001	1.58	1.48–1.69	<.0001
Ventilator dependent	Yes	84	650	1.13	0.89–1.43	0.284	1.13	0.88–1.43	0.32
Ascites	Yes	39	332	1.47	1.05–2.07	0.023	1.35	0.95–1.93	0.09
	No	1202	14,212	2.74	2.58–2.91	<.0001	1.55	1.46–1.65	<.0001
Chemotherapy	Yes	50	302	1.73	1.28–2.35	0.0003	1.06	0.76–1.46	0.72
	No	1191 (0.02)	14,242	2.74	2.58–2.90	<.0001	1.57	1.47–1.67	<.0001
Radiation	Yes	28	177	2.42	1.61–3.64	<.0001	1.37	0.83–2.25	0.21
	No	1213 (0.02)	14,367	2.73	2.57–2.89	<.0001	1.55	1.46–1.65	<.0001
CKD or on dialysis	Yes	57	420	1.54	1.16–2.04	0.0022	1.34	1.01–1.79	0.04
	No	1184 (0.02)	14,124	2.77	2.61–2.94	<.0001	1.55	1.46–1.65	<.0001
Malignancy	Yes	111	888	1.47	1.20–1.80	<.0001	1.23	0.99–1.52	0.06
	No	1130 (0.02)	13,656	2.75	2.58–2.92	<.0001	1.59	1.49–1.69	<.0001

Variables adjusted for: sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

4. Discussion

Our results suggest that there is an association between prolonged preoperative glucocorticoids use and postoperative VTE manifesting as DVT and/or PE. Previous data has already shown that glucocorticoid users had an increased risk of VTE, particularly PE [11,12]. This was also described in numerous medical settings such as Cushing's syndrome [6] and in diseases where glucocorticoids are part of the therapeutic regimen such as Acute Lymphoblastic Leukemia [13] and Multiple Myeloma [14]. In the surgical setting, several other studies

Table 4
Mortality and specific morbidities.

	Glucocorticoid intake n (OR) N = 58,667	No glucorticoids n (OR) N = 1,863,234	OR_{crude}	CI	p-Value	OR_{adj1}	CI	P-Value
Mortality[a]	2525 (4.30)	21,868 (1.17)	3.78	3.63–3.94	<.0001	1.42	1.35–1.49	<.0001
Cardiac[b]	852 (1.45)	11,665 (0.63)	2.33	2.18–2.50	<.0001	1.19	1.11–1.29	<.0001
Respiratory[c]	4094 (6.98)	44,220 (2.37)	3.08	2.98–3.18	<.0001	1.302	1.301–1.303	<.0001
Urinary Tract[d]	937 (1.60)	10,752 (0.58)	2.79	2.61–2.99	<.0001	1.4	1.30–1.50	<.0001
Wound[e]	2135 (3.64)	29,221 (1.57)	2.37	2.26–2.47	<.0001	1.58	1.51–1.66	<.0001
Sepsis[f]	1515 (2.58)	13,286 (0.71)	3.69	3.49–3.89	<.0001	1.51	1.42–1.60	<.0001

Variables adjusted for:

[a] Sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

[b] Sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

[c] Sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

[d] Sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

[e] Sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

[f] Sex, age, race, BMI, diabetes mellitus, alcohol, smoking, pneumonia, ascites, esophageal varices, congestive heart failure, myocardial infarction, previous cardiac surgery, previous peripheral vascular disease, acute renal failure, dialysis, coma, hemiplegia, cerebrovascular accident, central nervous system tumor, paraplegia, quadriplegia, disseminated cancer, open wound, bleeding disorder, chemotherapy, radiotherapy, prior operation within 30 days, albumin, ASA class, emergency case, type of anesthesia, inpatient status, operative time, and type of operation.

from the NSQIP demonstrated that these findings are translatable to surgical patients. In one study looking for modifiable risk factors for VTE after surgery for inflammatory bowel disease (IBD), chronic glucocorticoid use prior to operative intervention for IBD was shown to be such a risk factor [15]. Interestingly, another study looking at the risk factors and clinical impact of postoperative symptomatic VTE, also demonstrated that glucocorticoid use is an independent factor associated with a 1.5 fold (95% CI, 1.10–2.20) increased risk of VTE, very similar to the risk that we obtained [16]. To our knowledge, our study including 1,921,901 patients in the main analysis is the only one investigating the direct association between chronic glucocorticoid intake and postoperative VTE, our primary outcome. Our findings may open the door for a more thorough investigation, especially that glucocorticoid intake is a modifiable risk factor for VTE, a huge burden on patient overall health, postoperative recovery course and time as well as healthcare resources and cost [2–4]. Our results further highlight the need to explore this modifiable risk factor as it is not only associated with our primary outcome but several other secondary outcomes of paramount importance. We show in our analysis that preoperative glucocorticoid use for more than 30 days is associated with an increased risk in all-cause mortality and increased risks in cardiac, respiratory, urinary tract and wound adverse events respectively as well as an increased risk of sepsis. The association with sepsis and wound adverse events is concordant with the known inhibitory effect of prolonged glucocorticoid use on wound healing and immune functions. The relationship with all-cause mortality, cardiac and respiratory adverse events on the other hand might be explained by the association with our primary outcome VTE. Interpreting our findings is a challenging task since VTE is usually caused by an interplay of several factors, which makes causal relationships difficult to draw. The retrospective nature of the NSQIP database makes the latter even more difficult. Other database related limitations to our analysis is the inability to establish a dose–effect profile for our exposure of interest or explore whether different routes of administration of glucocorticoids or duration of use have variable effects on the outcomes that we have considered since these variables are not recorded. This is important as duration of use as well as dose and route of glucocorticoid administration have been shown to have an effect on the risk of development of VTE in previous studies [11,12]. Other inherent missing information from our database that might lead to unmeasured confounding include detailed anticoagulation regimens and history of hypercoagulability disorders as well as limited history and follow-up to 30 perioperative days. We believe that follow-up studies should focus on exploring the detailed mechanism behind our findings and a deeper understanding of VTE biology with an emphasis on potential interference with the normal physiologic function of the clotting cascade as this has been previously reported [17,18].

5. Conclusion

Our study shows that prolonged preoperative glucocorticoid use for longer than 30 days is associated with an increased risk of postoperative VTE, all-cause mortality and other comorbidities. This is important since glucocorticoid use is a modifiable risk factor and a true understanding of this association might lead to improved outcomes for surgical patients. The latter serves the core essence of surgical practice and the NSQIP database: quality improvement in surgery and patient safety.

Conflict of interests

The authors state that they have no conflict of interest.

Author contributions

Anthony Haddad M.D. and Rami Kantar M.D. were responsible for the conception, design, and tabulation of the data. In addition they were both responsible for drafting the abstract and manuscript.

Hani Tamim PhD was responsible for data analysis.

Faek Jamali M.D. provided a thorough review and input based on his expertise in the surgical field.

Ali Taher M.D. PhD provided his mentorship along the way in addition to a thorough review and input based on his expertise in the discipline of Hematology and the field of thrombosis.

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