CLINICAL ARTICLE

Patients Undergoing Primary Total Joint Arthroplasty with Primary Hypercoagulable States

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Objective: To analyze perioperative complications, resource consumption, and inpatient mortality of patients who receive total joint arthroplasty (TJA) with a concomitant diagnosis of a primary hypercoagulable state (PHS). The following questions were posed in the present paper. First, do patients undergoing TJA with PHS have increased risk of deep venous thrombosis (DVT), pulmonary embolism (PE), and periprosthetic joint infection (PJI)? Second, what other in-hospital complications are more likely among PHS patients undergoing TJA? Third, do TJA patients with PHS usually consume greater in-hospital resources? Fourth, do PHS patients suffer higher mortality rates compared to non-PHS patients? Finally, have PHS patients received proper anticoagulant management in past arthroplasties?

Methods: The National Inpatient Sample (NIS) database for the years between 2003 and 2014 was searched to identify patients undergoing primary TJA. Patients with PHS were identified with the ICD-9-CM code 289.81. The χ^2-test, the Pearson test, and adjusted multivariate regression analysis were performed to evaluate the difference and odds ratios between the positive and negative diagnosis groups.

Results: From 2003 to 2014, a total of 2,044,356 patients were identified in the NIS as undergoing primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) in the United States. A total of 4664 patients (0.2%) were identified as having PHS. Compared with the non-PHS group, TJA patients with PHS had a higher risk of DVT (THA: odds ratio [*OR*] = 8.343, 95% CI: 5.362–12.982, $P < 0.001$; TKA: *OR* = 4.712, 95% *CI*: 3.560–6.238, $P < 0.001$) but did not have increased risk of PE (THA: *OR* = 1.306, 95% *CI*: 0.48–3.555, $P = 0.602$; TKA: *OR* = 1.143, 95% *CI*: 0.687–1.903), and only PHS patients in the THA group had higher risks of inpatient mortality (*OR* = 3.184, 95% *CI*: 1.348–7.522, $P = 0.008$) and periprosthetic joint infection (*OR* = 3.343, 95% *CI*: 1.084–10.879, $P = 0.036$). In addition, PHS patients had extended length of stay, higher total costs, and increased risks of certain other complications, such as peripheral vascular disease, hemorrhage, and thrombophlebitis.

Conclusion: In the present study, PHS patients had higher risks of DVT, greater in-hospital resource consumption, and certain other perioperative complications. However, PHS was not associated with increased risk of PE in TJA patients in the United States between 2003 and 2014. While potential hazards of PHS have already been recognized, the present study revealed additional concerns and demonstrated that further improvements in the perioperative management of patients with hereditary hypercoagulable disorders are essential.

Key words: Perioperative complication; Primaryhypercoagulable state; Resource consumption; Total joint arthroplasty

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Introduction

Primary hypercoagulable states (PHS), also called inherited thrombophilia, are a series of genes-related thrombophilia disorders. Activated protein C resistance, antithrombin III deficiency, factor V Leiden mutation, lupus anticoagulant, protein C deficiency, protein S deficiency, and prothrombin gene mutations are currently commonly recognized to be hereditary thrombophilia diseases[1–5], and they are listed within the description of PHS in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Generally speaking, patients may be candidates for screening for hypercoagulable states if they have: a family history of abnormal blood clotting; abnormal blood clotting at a young age (less than 50 years of age); thrombosis in unusual locations or sites, such as veins in the arms, liver, intestines, kidney, or brain; blood clots that occur without a clear cause (idiopathic); blood clots that recur; a history of frequent miscarriages; and stroke at a young age.

For multiple surgical procedures, such as obstetric surgeries, many studies have indicated that thrombophilia disorders increase the risk of deep vein thrombosis (DVT) or pulmonary embolism (PE)[6,7]. The refinements of anesthesia, operative techniques, and chemical and physical therapies have reduced the incidence of thromboembolic complications after arthroplasty operations[8–12]. Despite this progress, some patients still inevitably experience DVT, and it has been hypothesized that there may be a genetic susceptibility[13–15]. PE is one of the major fatal perioperative complications of orthopaedic surgeries[16]. Prosthesis joint infection (PJI) often leads to failure of arthroplasty and the need for revision. Blood-related disorders are suggested to be the potential risk factor for not only PE and PJI but also DVT[17–19]. Furthermore, arthroplasty will unavoidably satisfy Virchow's triad of three elements: vein stasis, endothelial injury, and hypercoagulability in PHS patients[20].

Although PHS could be a vital risk factor of thrombosis events and other adverse events during an orthopaedic operation, whether PHS could substantially induce significant adverse effects in clinical practice remains controversial. Moreover, there are few published studies on the impacts of PHS in orthopaedic operations. On one hand, there are extremely low incidences of fatal DVT, PE, and mortality in patients undergoing primary TKA or THA. On the other hand, the same low prevalence of PHS is exhibited in the general population. Therefore, it could have been rather difficult for previous researchers to carry out a comprehensive and representative evaluation in patients receiving primary total joint arthroplasty (TJA) with a diagnosis of PHS. In addition, these previous studies could usually only survey a limited number of patients, and their patient samples were generally from a single hospital. As a result, conclusions drawn by previous researchers on PHS in arthroplasty operations might not be representative. Taking into account the multiple drawbacks of the previous research, evaluating the real impacts of PHS in patients undergoing TJA is necessary.

Following general anticoagulant guidelines, whether primary hypercoagulability has significant adverse impacts on perioperative outcomes in recent clinical practice remains unclear and debated[21,22]. The conclusions of previous research vary, particularly regarding the risks of PHS on DVT and PE. Furthermore, given that genetic predisposition could be one of the intrinsic factors, moderate or radical strategies of thrombus prophylaxis for patients undergoing primary TJA remain controversial too[23]. If the adverse impacts of PHS are underestimated, significant increased risks of thrombosis-related complications during the perioperative period may occur in PHS patients. Conversely, if excess aggressive thrombosis prophylaxis is carried in PHS patients, other adverse complications brought about by overuse of anticoagulant may occur, such as hemorrhage around the wound, acute postoperative anemia, and ecchymosis.

However, in retrospectively analyzing a large nationally-representative database, we were able to observe a sufficient number of PHS patients. The objectives of our study were to examine: (i) whether PHS was an independent risk factor for DVT, PE, prosthesis joint infection, and other common and blood-related perioperative complications; (ii) whether patients undergoing primary TJA with PHS consumed greater in-hospital resources (total cost and length of stay) compared to general patients; (iii) whether there was a higher in-hospital mortality rate in TJA patients who had a concomitant diagnosis of PHS; and (iv) whether PHS patients recieved proper anticoagulant management during the perioperative period in the United States between 2003 and 2014.

We hypothesized that although surgeons already knew their patients had genetic hypercoagulability, PHS remained an independent risk factor for perioperative complications, resource consumption, and in-hospital mortality. Therefore, improvements in anticoagulant strategies for PHS patients are essential.

In sum, we hope that the present study will provoke thought and inspiration for orthopaedic surgeons to implement targeted and personal treatment for PHS patients.

Methods

Data Source

Data from 2003 to 2014 were obtained from the National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality. The range of years selected within the study was based on the PHS code, which was initially recorded in the NIS database in 2003.

A search was conducted in the NIS database using the ICD-9-CM procedure codes 81.51 and 81.54, respectively, for patients receiving primary total knee arthroplasty (TKA) or total knee arthroplasty (TKA) between 2003 and 2014. Patients with a concomitant diagnosis of a pathologic

fracture, infections around a device, implant or graft, or primary malignant bone neoplasm were excluded.

Participant Criteria

First, patients with PHS were identified by the ICD-9-CM code 289.81. The enrolled patients were divided into four cohorts: patients receiving TKA or THA diagnosed with PHS or not. Second, in the present study, we compared PHS and non-PHS patients to analyze the impacts of PHS on perioperative risks and resource consumption during a TJA. Third, to compare the perioperative complication risks of PHS patients compared to non-PHS patients, the incidences of the following perioperative complications were extracted: central nervous system disease, gastrointestinal disease, peripheral vascular disease, arrhythmia, acute renal failure, pneumonia, and acute postoperative anemia (Table 1). The in-hospital mortality rate is also shown in Table 1. As in previous studies, we used length of stay and total cost to measure the in-hospital resource consumption. Information on demographic characteristics was also extracted, including age, sex, race, type of admission, type of pay, and location/region/volume/teaching status of the hospital. Elixhauser comorbidities were used in the present study, which are considered to more accurately contribute to morality than Deyo–Charlson comorbidities do[24–26]. We used a national representative database to retrospectively analyze the perioperative complication risks and resource consumption in PHS patients compared to non-PHS patients.

Statistical Analysis

To compare the outcomes between PHS and non-PHS patients, the Pearson χ^2-test was performed to identify the differences of the counting variables (e.g. sex and race). Student's *t*-test was calculated for continuous variables (e.g. age, total charge, and length of stay). The odds ratio (*OR*) and the 95% confidence interval (*CI*) for every complication observed in the study were also calculated, and the negative-diagnosis group was compared as a control. A *P*-value of <0.05 was considered statistically significant and a value of $OR > 1$ represented an increased risk of suffering the complication; in contrast, $OR < 1$ was considered a reduced risk.

Multivariate logistic regression analysis was performed to assess the associations among perioperative complications, early outcomes, preexisting comorbidities, and PHS. The covariates of regression analysis included age, gender, race, type of admission, and Elixhauser comorbidities. Similar to previous studies, The overpass 75th percentile of the LOS

TABLE 1 Complication rate and resource consumption of patients undergoing primary THA or TKA with or without PHS

	Primary THA			Primary TKA		
Complication rate and resource consumption	Non-PHS	PHS	*P*-value	Non-PHS	PHS	*P*-value
Acute postoperative anemia	24.20%	29.11%	0.001	19.16%	23.95%	0.001
Blood transfusion	22.71%	23.28%	0.597	15.73%	15.41%	0.629
Arrhythmia	10.29%	12.59%	0.003	9.89%	10.48%	0.269
Total surgical complications	7.84%	11.28%	0.001	6.09%	8.25%	0.001
Phlebitis; thrombophlebitis and thromboembolism	3.30%	46.69%	0.001	3.80%	50.61%	0.001
Total device complications	2.01%	2.89%	0.015	0.67%	0.92%	0.077
Acute renal failure	1.75%	3.08%	0.001	1.48%	2.20%	0.001
Hemorrhage/hematoma/seroma	0.95%	1.97%	0.001	0.67%	1.11%	0.002
Pneumonia	0.61%	0.85%	0.224	0.49%	0.89%	0.001
Gastrointestinal	0.57%	0.98%	0.032	0.42%	0.57%	0.2
Occlusion or stenosis of precerebral arteries	0.50%	0.46%	0.837	0.40%	0.64%	0.035
Deep venous thrombosis	0.18%	1.84%	0.001	0.36%	2.29%	0.001
Central nervous system disease	0.13%	0.20%	0.445	0.10%	0.40%	0.001
Sepsis	0.13%	0.33%	0.038	0.08%	0.13%	0.348
Urinary tract infection	0.13%	0.20%	0.469	0.16%	0.16%	0.993
Acute cerebrovascular disease	0.13%	0.20%	0.495	0.09%	0.41%	0.001
Pulmonary embolism	0.12%	0.33%	0.021	0.29%	0.89%	0.001
Other and ill-defined cerebrovascular disease	0.12%	0.33%	0.015	0.09%	0.29%	0.001
Shock	0.11%	0.20%	0.281	0.05%	0.13%	0.074
Peripheral vascular disease	0.06%	0.33%	0.001	0.16%	0.57%	0.001
Periprosthetic joint infection (PJI)	0.05%	0.33%	0.001	0.03%	0.03%	0.958
Wound debridement and irrigation	0.04%	0.46%	0.001	0.05%	0.03%	0.772
Aortic and peripheral arterial embolism or thrombosis	0.02%	0.07%	0.317	0.04%	0.06%	0.471
Disruption of surgical wound	0.01%	0.00%	0.634	0.07%	0.03%	0.382
Postoperative infection	0.00%	0.00%	0.907	0.00%	0.00%	0.9
Death	0.17%	0.39%	0.036	0.08%	0.10%	0.76
Total cost (USD: Mean)	48,505.18	57,425.86	0.001	45,610.48	51,645.27	0.001
Length of stay (Day: Mean)	3.52	4.01	0.001	3.38	3.66	0.001

THA, total hip arthroplasty; TKA, total knee arthroplasty; PHS, primary hypercoagulable state.

and total hospital charges were defined as a prolonged stay and a higher cost, respectively[27].

All statistical analyses performed in the study utilized SPSS version 25 (IBM, Armonk, NY, USA).

Results

Demographics and Comorbidities

Demographics

Between 2003 and 2014, 1524 and 3140 patients undergoing primary THA or TKA were concomitantly identified as having PHS, respectively. PHS patients were more likely to be younger, female (PHS: 59.78%–68.31% *vs* control: 56.30%–63.41%), and White (PHS: 90.19%–90.43% *vs* control: 83.59%–86.69%), and to receive surgeries in teaching hospitals (PHS: 51.72%–56.64% *vs* control: 42.89%–48.50%). However, neither admission type nor pay type in the THA group show a significant difference, but there were small differences in the TKA group (Table 2) .

Comorbidities

Regarding comorbidities, approximately half of the comorbidities exhibited no statistical differences of incidences between the PHS and non-PHS cohort in both THA and TKA groups (Table 3).

Risks of Deep Venous Thrombosis, Pulmonary Embolism, and Periprosthetic Joint Infection

Incidences

The PHS patients in THA and TKA groups suffered higher rates of DVT (THA: 1.84% *vs* 0.18%, $P < 0.001$; TKA: 2.29% *vs* 0.36%, $P < 0.001$) and PE (THA: 0.33% *vs* 0.13%, $P = 0.021$; TKA: 0.89% *vs* 0.29%, $P < 0.001$) compared to general patients. Only PHS patients in the THA group showed a significant difference of incidence for periprosthetic joint infection (THA: 0.33% [PHS] *vs* 0.05% [control], $P < 0.001$; TKA: 0.03% [PHS] *vs* 0.03% [control], $P = 0.958$) (Table 1).

Odds Ratios

PHS was an independent risk factor for DVT for both THA (*OR* = 8.343; 95% *CI*: 5.362–12.982; $P < 0.001$) and TKA (*OR* = 4.712; 95% *CI*: 3.560–6.238; $P < 0.001$) patients. However, neither THA nor TKA patients with PHS had an increased OR for PE (THA: *OR* = 1.306, 95% *CI*: 0.48–3.555, $P = 0.602$; TKA: *OR* = 1.143, 95% *CI*: 0.687–1.903, $P = 0.606$). Patients in the THA group were at increased risk of periprosthetic joint infection (*OR* = 3.343; 95% *CI*: 1.084–10.879; $P = 0.036$), while in the TKA group, the incidence had no statistical difference.

Incidences and Odds Ratios of Other Perioperative Complications

Primary Total Hip Arthroplasty

Table 1 reveals that significant higher incidences existed for the following complications among PHS patients undergoing THA: gastrointestinal complications (0.98% *vs* 0.57%; $P = 0.032$), peripheral vascular disease (0.33% *vs* 0.06%; $P < 0.001$), arrhythmia (12.59% *vs* 10.29%; $P = 0.003$), acute renal failure (3.08% *vs* 1.75%; $P < 0.001$), acute postoperative anemia (29.11% *vs* 24.20%; $P < 0.001$), hemorrhage/hematoma/seroma (1.97% *vs* 0.95%; $P < 0.001$), wound debridement (0.39% *vs* 0.03%; $P < 0.001$), irrigation (0.07% *vs* 0.01%; $P = 0.006$), and other and ill-defined cerebrovascular disease (0.33% *vs* 0.12%; $P = 0.015$). Other complications observed in the study but with no statistical differences can also be seen in Table 1.

However, PHS was not an independent risk factor for all the complications mentioned above. Only gastrointestinal complications (*OR* = 1.852, 95% *CI*: 1.040–3.299, $P = 0.036$), hemorrhage/hematoma/seroma (*OR* = 2.025, 95% *CI*: 1.319–3.110, $P < 0.001$), wound debridement (*OR* = 6.121, 95% *CI*: 2.202–17.017, $P < 0.001$) and irrigation (*OR* = 16.197, 95% *CI*: 2.159–121.520, $P = 0.007$), other and ill-defined cerebrovascular disease (*OR* = 3.217, 95% *CI*: 1.319–7.848, $P = 0.010$), total surgical complications (*OR* = 1.405, 95% *CI*: 1.174–1.681, $P < 0.001$), as well as phlebitis (*OR* = 24.009, 95% *CI*: 21.396–26.942, $P < 0.001$) exhibited higher *OR*, of which the *OR* of phlebitis was significantly high (Table 4).

Primary Total Knee Arthroplasty

Details of the incidences of complications can be seen in Table 1. As shown in Table 5, patients with PHS in the TKA group had higher OR for central nervous system complications (*OR* = 6.403, 95% *CI*: 3.566–11.495, $P < 0.001$), peripheral vascular disease (*OR* = 2.822, 95% *CI*: 1.584–5.026, $P < 0.001$), pneumonia (*OR* = 1.627, 95% *CI*: 1.048–2.527, $P = 0.030$), acute postoperative anemia (*OR* = 1.168, 95% *CI*: 1.061–1.286, $P = 0.002$), DVT (*OR* = 4.712, 95% *CI*: 3.560–6.238, $P < 0.001$), hemorrhage/hematoma/seroma (*OR* = 2.025, 95% *CI*: 1.319–3.110, $P < 0.001$), urinary tract infection (*OR* = 1.287, 95% *CI*: 1.019–1.627, $P = 0.034$), acute cerebrovascular disease (*OR* = 5.534, 95% *CI*: 3.039–10.079, $P < 0.001$), other and ill-defined cerebrovascular disease (*OR* = 3.217, 95% *CI*: 1.319–7.848, $P = 0.010$), total surgical complications (*OR* = 1.405, 95% *CI*: 1.174–1.681, $P < 0.001$), as well as phlebitis (*OR* = 24.932, 95% *CI*: 21.029–26.993, $P < 0.001$), which showed a notable higher *OR*, as in the THA group.

Resource Consumption and Mortality

Resource Consumption

Total cost (unit: USD; THA: 48505.18 ± 28888.60 *vs* 57425.86 ± 38935.33, $P < 0.001$; TKA: 45610.48 ± 27028.72 *vs* 51645.27 ± 32184.13, $P < 0.001$) and length of stay (unit:

TABLE 2 Demographics of patients undergoing primary THA or TKA diagnosed with or without PHS

	Primary THA (*n* = 664,933)			Primary TKA (*n* = 1,379,423)		
Demographic	Non-PHS	PHS	*P*-value	Non-PHS	PHS	*P*-value
Patient number	663.409 (99.77%)	1,524 (0.23%)		1376283 (99.77%)	3.140 (0.23%)	
Sex			0.006			0.001
Male	43.70%	40.22%		36.86%	31.69%	
Female	56.30%	59.78%		63.14%	68.31%	
Age group			0.001			0.001
0–44	5.36%	7.15%		1.81%	3.06%	
45–54	14.35%	17.84%		11.42%	13.76%	
55–64	25.96%	28.26%		28.92%	33.09%	
65–74	28.85%	29.38%		34.77%	35.19%	
≥75	25.48%	17.38%		23.08%	14.90%	
Race			0.013			0.001
White	71.01%	74.75%		68.47%	74.62%	
Black	5.78%	4.52%		6.01%	3.76%	
Hispanic	2.53%	1.70%		4.26%	1.46%	
Asian or Pacific Islander	0.68%	0.39%		0.97%	0.29%	
Native American	0.25%	0.13%		0.37%	0.38%	
Other	1.67%	1.38%		1.84%	2.01%	
Missing	18.09	17.11%		18.09%	17.48%	
Admission type			0.654			0.026
Non-elective	9.14%	8.80%		6.08%	5.13%	
Elective	90.86%	91.20%		93.92%	94.87%	
Hospital location			0.071			0.001
Rural	10.36%	8.95%		12.38%	10.50%	
Urban	89.64%	91.05%		87.62%	89.50%	
Bed size			0.334			0.84
Small	18.10%	17.96%		18.83%	18.67%	
Medium	25.16%	23.62%		25.82%	25.46%	
Large	56.75%	58.42%		55.35%	55.87%	
Hospital teaching status			0.001			0.001
Non-teaching	51.50%	43.36%		57.11%	48.28%	
Teaching	48.50%	56.64%		42.89%	51.72%	
Pay type			0.08			0.001
Medicare	53.25%	50.46%		55.95%	52.64%	
Medicaid	3.49%	3.35%		2.84%	2.20%	
Private insurance	39.91%	42.19%		37.45%	41.81%	
Self-pay	0.79%	0.66%		0.44%	0.22%	
No charge	0.14%	0.07%		0.08%	0.03%	
Other	2.42%	3.28%		3.24%	3.09%	

THA, total hip arthroplasty; TKA, total knee arthroplasty; PHS, primary hypercoagulable state.

day; THA: 3.52 ± 2.327 *vs* 4.01 ± 3.772, $P < 0.001$; TKA: 3.38 ± 1.739 *vs* 3.66 ± 2.494, $P < 0.001$) for PHS patients were all higher or longer than in the negative-diagnosis group in both THA and TKA cohorts (Table 2). In addition, PHS was an independent risk factor of extended length of stay (THA: *OR* = 1.776, 95% *CI*: 1.586–1.990, $P < 0.001$; TKA: *OR* = 1.891, 95% *CI*: 1.626–2.199, $P < 0.001$) and higher cost (THA: *OR* = 1.214, 95% *CI*: 1.112–1.325, $P < 0.001$; TKA: *OR* = 1.262, 95% *CI*: 1.112–1.432, $P < 0.001$) for both THA and TKA patients (Tables 4 and 5).

Mortality

Table 4 shows that PHS was an independent risk factor of mortality (incidence: 0.39% *vs* 0.17%; *OR* = 3.184, 95% *CI*: 1.348–7.522, $P = 0.008$) in THA patients. In the TKA group, PHS patients did not exhibit a higher *OR* of inpatient mortality (Incidence: 0.10% *vs* 0.08%; *OR* = 1.494, 95% *CI*: 0.468–4.766, $P = 0.498$) (Table 5).

Discussion

Importance of Further Knowledge of Primary Hypercoagulable States in Total Joint Arthroplasty

The number of patients undergoing TJA is increasing yearly. Further knowledge of potential risk factors for perioperative complications would be helpful for perioperative management. For orthopaedic operations, individual genetic heterogeneity (e.g. having PHS) could be one of the factors contributing to perioperative complications, not just DVT and PE. However, previous studies have typically investigate extremely small samples and only concentrated on the impacts of PHS on DVT and PE. Hence, using a large

TABLE 3 Comorbidities in patients undergoing primary THA or TKA with or without PHS

	Primary THA			Primary TKA		
Comorbidity	Non-PHS	PHS	*P*-value	Non-PHS	PHS	*P*-value
Hypertension	58.32%	56.50%	0.149	66.66%	63.31%	0.001
Chronic pulmonary disease	13.94%	16.01%	0.02	14.29%	18.34%	0.001
Deficiency anemias	13.70%	15.49%	0.043	12.35%	15.19%	0.001
Obesity	13.16%	18.77%	0.001	19.36%	26.72%	0.001
Diabetes, uncomplicated	12.94%	12.20%	0.395	19.23%	17.68%	0.028
Hypothyroidism	12.74%	15.03%	0.008	14.91%	18.54%	0.001
Depression	10.12%	14.30%	0.001	11.52%	17.58%	0.001
Arrhythmia	8.93%	11.21%	0.002	8.56%	8.76%	0.686
Fluid and electrolyte disorders	8.67%	11.48%	0.001	7.74%	8.57%	0.081
Valvular disease	3.98%	4.86%	0.08	3.60%	4.68%	0.001
Rheumatoid arthritis/collagen vascular diseases	3.77%	9.45%	0.001	3.66%	8.25%	0.001
Other neurological disorders	3.42%	5.77%	0.001	3.45%	5.80%	0.001
Renal failure	3.39%	7.22%	0.001	3.20%	5.41%	0.001
Congestive heart failure	2.85%	3.41%	0.188	2.56%	2.61%	0.854
Peripheral vascular disorders	2.19%	2.95%	0.042	1.86%	3.41%	0.001
Coagulopathy	2.07%	6.43%	0.001	1.71%	4.90%	0.001
Chronic blood loss anemia	1.84%	1.71%	0.689	1.59%	1.97%	0.082
Psychoses	1.67%	1.84%	0.604	1.80%	2.83%	0.001
Alcohol abuse	1.57%	1.84%	0.405	0.75%	0.80%	0.757
Diabetes with chronic complications	1.10%	1.18%	0.756	1.55%	1.62%	0.733
Liver disease	0.96%	2.03%	0.001	0.79%	1.18%	0.013
Pulmonary circulation disorders	0.76%	2.36%	0.001	0.84%	2.74%	0.001
Drug abuse	0.64%	1.31%	0.001	0.38%	0.48%	0.366
Solid tumor without metastasis	0.58%	0.46%	0.542	0.41%	0.41%	0.993
Weight loss	0.50%	1.25%	0.001	0.20%	0.41%	0.006
Paralysis	0.38%	1.12%	0.001	0.26%	0.70%	0.001
Lymphoma	0.37%	0.46%	0.58	0.21%	0.25%	0.614
Metastatic cancer	0.29%	0.33%	0.776	0.07%	0.03%	0.442
AIDS	0.10%	0.30%	0.057	0.00%	0.10%	0.045
Peptic ulcer disease excluding bleeding	0.02%	0.00%	0.562	0.02%	0.03%	0.793

THA, total hip arthroplasty; TKA, total knee arthroplasty; PHS, primary hypercoagulable state.

TABLE 4 Multivariate logistic regression analysis of patients undergoing primary THA with PHS

Complication and outcome	*OR*	95% *CI*		*P*-value
Thrombophlebitis and thromboembolism	24.009	21.396	26.942	0.001
Deep venous thrombosis	8.343	5.362	12.982	0.001
Wound debridement/irrigation	6.121	2.202	17.017	0.001
Peripheral vascular disease	5.609	2.058	15.286	0.001
Periprosthetic joint infection	3.434	1.084	10.879	0.036
Other and ill-defined cerebrovascular disease	3.217	1.319	7.848	0.01
Mortality	3.184	1.348	7.522	0.008
Hemorrhage/hematoma/seroma	2.025	1.319	3.11	0.001
Length of stay	1.891	1.626	2.199	0.001
Gastrointestinal	1.852	1.04	3.299	0.036
Sepsis	1.457	0.563	3.772	0.438
Total surgical complications	1.405	1.174	1.681	0.001
Pulmonary embolism	1.306	0.48	3.555	0.602
Total device complications	1.294	0.915	1.831	0.145
Total charge	1.262	1.112	1.432	0.001
Acute renal failure	1.188	0.831	1.699	0.344
Acute postoperative anemia	1.079	0.946	1.231	0.257
Arrhythmia	1.036	0.789	1.362	0.797

CI, confidence interval; OR, odds ratio; THA, total hip arthroplasty; PHS, primary hypercoagulable state.

TABLE 5 Multivariate logistic regression analysis of patients undergoing primary TKA with PHS

Complication and outcome	*OR*	95% *CI*		*P*-value
Thrombophlebitis and thromboembolism	24.932	23.03	26.993	0.001
Central nervous system disease	6.403	3.566	11.495	0.001
Acute cerebrovascular disease	5.534	3.039	10.079	0.001
Deep venous thrombosis	4.712	3.56	6.238	0.001
Other and ill-defined cerebrovascular disease	2.879	1.362	6.083	0.006
Peripheral vascular disease	2.822	1.584	5.026	0.001
Hemorrhage/hematoma/seroma	1.891	1.289	2.774	0.001
Length of stay	1.776	1.586	1.99	0.001
Pneumonia	1.627	1.048	2.527	0.03
Mortality	1.494	0.468	4.766	0.498
Occlusion or stenosis of precerebral arteries	1.41	0.856	2.323	0.177
Urinary tract infection	1.287	1.019	1.627	0.034
Total surgical complications	1.285	1.108	1.49	0.001
Acute renal failure	1.253	0.948	1.656	0.113
Total charge	1.214	1.112	1.325	0.001
Acute postoperative anemia	1.168	1.061	1.286	0.002
Pulmonary embolism	1.143	0.687	1.903	0.606

administrative database, the present study aims to address such drawbacks.

Risks of Deep Venous Thrombosis and Pulmonary Embolism in Patients undergoing Total Joint Arthroplasty with Primary Hypercoagulable States

Consistent with our hypothesis, TJA patients with PHS suffered increased risk of DVT and higher burdens from certain perioperative complications, with the exception of PE. Genetic thrombophilia abnormalities are identified as risk factors for DVT and PE among general patients investigated by multiple researchers[28]. Nevertheless, how primary hereditary hypercoagulable states affect perioperative complications and outcomes after TJA in practice remains unclear[13,15]. A single-center prospective study demonstrated that factor V Leiden, prothrombin G20210A, and MTHFRC677T mutations are not significant risk factors for DVT in patients receiving lower extremity arthroplasty[22]. However, another study reached contrasting conclusions[29]. A pilot study selected 43 TKA patients who had a history of DVT or PE prior to arthroplasties to check the coagulation-related genes, and found that these patients had a higher frequency of hereditary abnormalities[21]. However, this study did not conduct a comparison with patients without a history of DVT or PE. In another matched comparison study, 14 patients with documented PE after THA and 14 patients without any clinical indication of thromboembolism were compared. A similar conclusion was reached that genetic thrombophilia and hypo-fibrinolysis were more frequent in patients who had had PE after total hip arthroplasty[30]. Therefore, genetic predispositions are associated with increased odds of the occurrence of embolization events. However, these previous published studies usually investigated a rather small sample of patients, such as the 14 or 44 patients mentioned above, and patient samples were usually from a single or limited number of hospitals[13,22,31,32]. Even worse, conclusions of the actual impacts of PHS for orthopaedic surgeries vary from different studies, because they were surveyed among different selected patient cohorts or with dissimilar adverse outcome criterions[5,21,33]. Using the largest publicly available all-payer inpatient care stratified sample database in the United States, which contains more than seven million hospital stays, our results reveal that in recent clinical practice, PHS has merely been an independent risk factor for DVT but not for PE. Within our study, it seemed that inherited thrombophilia abnormalities were merely associated with increased risks of thrombogenesis, such as thrombophlebitis, thromboembolism, and DVT, but did not reach the point of incurring destructive outcomes in clinical practice, such as PE.

Risks of Other Perioperative Complications in Patients with Primary Hypercoagulable States Undergoing Total Joint Arthroplasty

Most previous researchers have merely concentrated on the risks of DVT and PE; few have paid attention to other common or blood-related complications that might occur as a result of PHS. However, by analyzing a large database, our research was able to identify numerous potential affected perioperative complications. In addition, we found PHS patients had significantly high incidence (PHS: 46.69% to 50.61% *vs* non-PHS: 3.30% to 3.80%) and risk of phlebitis (*OR* 24.009 to 24.932). This result may strongly indicate that PHS patients are at a higher risk for DVT after surgery in the long term under the current strategy of anticoagulant prevention because non-symptomatic thrombophlebitis is usually associated with an increased risk of developing DVT[34–36]. Subsequently, central nervous system complications, acute cerebrovascular disease, and peripheral vascular disease also exhibited higher *OR* in PHS patients in both THA and TKA groups, which may be the secondary adverse outcomes of the significant high risk of thrombophlebitis

exhibited above. Arthroplasty surgeons should pay more attention to the perioperative complications mentioned above, particularly for patients who have inherent hypercoagulability. There was also a higher risk of urinary tract infection, acute renal failure, and surgical complications, but we could not determine their latent relationships with PHS.

Evaluation of Anticoagulation Management in Primary Hypercoagulable State Patients in Past Arthroplasties

Did PHS patients undergoing TJA receive equally efficient and appropriate thrombus prophylaxis treatment compared to general patients between 2003 and 2014 in the United States? Interestingly, it appears that the approach taken for PHS patients might have been too radical. For instance, we found that TJA patients with primary thrombophilia abnormalities were at higher risk of acute operative anemia, hemorrhage, and cerebrovascular disease. Indeed, universal prophylactic anticoagulation prior to surgery and its potential adverse effects have caused much controversy in orthopaedic surgeries[37,38], and several studies indicate that application of anticoagulants would increase the risk of bleeding-related complications, such as hematoma and ecchymosis[23,39]. Subsequently, such bleeding events will increase the risk of infection-related complications, which was also reflected in our study. Furthermore, it appears that PHS has a greater impact on THA patients than TKA patients because THA patients are additionally more likely to suffer hemorrhage-related complications and require irrigation and debridement of wounds. These complications might subsequently result in increased risk of infection, such as the higher risk of periprosthetic joint infection in THA patients within our study. Although we do not have further information about the utilization of anticoagulants for patients within the study, our research is the first to reflect this potentially inappropriate anticoagulant prophylaxis strategy applied in past arthroplasties in the United States. This deserves more attention and further improvement from arthroplasty surgeons.

Resource Consumption in Primary Hypercoagulable State Patients

Heavier economic burden for PHS patients was exhibited not only in the present study but also in other research that utilized thromboprophylaxis therapy, expensive genetic screening tests, or both to reduce the potential risks of PHS[40]. Higher cost and longer hospitalizations for PHS patients can be attributed to the additional monitoring and adequate embolism prophylaxis, the prolonged observation period after arthroplasty of PHS patients, and the higher burden of perioperative complications demonstrated in the present study.

Limitations

Studies using a large database have inherent limitations. First, only perioperative complications were examined in the present study. We do not have long-term follow-up data on specific complications; they may be underestimated during the perioperative period as they often occur after discharge from hospital; thus, further studies on this aspect are needed. Second, we compared PHS patients with a general cohort of primary TJA patients; thus, the results should be compared with the overall cohort of TJA patients. Third, further research on specific abnormalities of PHS could not be performed in this study, as the ICD-9-CM system does not have a further classification for PHS. Fourth, some PHS patients in the study were incorrectly enrolled in the PHS-negative group due to the record bias of a database. This may increase the risk of false negatives, but, conversely, it may minimize the risk of false positives. However, this research is mainly concerned with positive outcomes; thus, this bias might not be particularly influential. Finally, we could not identify whether patients within the study all received a universal or active anticoagulant treatment. However, the major objective of our study was to determine the real impacts of PHS in past practical arthroplasties. Although PHS patients had a higher probability of receiving additional anticoagulant therapy, we still obtained the result that PHS patients were more likely to develop DVT, while they were not at higher risk of PE.

Strengths

Nevertheless, the National Inpatient Sample (NIS) database's large sample size of patients is ideal for developing national and regional estimates and enables analyses of rare conditions, uncommon treatments, and special populations[41], such as patients with PHS. Most importantly, patients in the NIS database were part of a stratified sample from approximately 1000 hospitals, which were chosen randomly according to stratum to achieve a sample of approximately 20% of the hospitals in each stratum. In brief, patients in our study were more representative than in previous studies. Patient samples were selected from a single or several hospitals and were few in number. Furthermore, with the exception of this study, many researchers have used the NIS database to estimate the nationwide trend, epidemiology, perioperative outcomes, and complications in TJA patients in the United States[42–44].

Conclusion

Despite the risk factors of thrombogenesis events being clear and anticoagulant strategies having improved, our research reveals that TJA patients with hereditary hypercoagulability not only suffer higher risks of thrombotic events but also have higher burdens from other perioperative complications and resource consumption. The anticoagulant strategy applied in the past for PHS patients might not have been appropriate. In sum, additional and improved perioperative treatment for PHS patients is necessary.

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