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Does Polycythemia Vera Increase Risk of Postoperative Complications Following Primary Total Joint Arthroplasty? A Retrospective Matched Control Cohort Study of 6932 Polycythemia Vera Patients

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ABSTRACT

Background: There is sparsity of data on outcomes following joint arthroplasty among polycythemia vera (PV) patients. The aim of this study is to evaluate postoperative outcomes following primary total knee (TKA) and hip (THA) arthroplasty among PV patients.

Methods: A retrospective Medicare database review identified 6932 PV patients who underwent a primary total joint arthroplasty (4643 TKAs and 2289 THAs) from 2006 to 2013. A comparison of hospital length of stay, mortality, and the diagnosis of surgical site infections (SSIs), stroke, myocardial infarction, acute pulmonary embolism (PE), deep vein thrombosis (DVT), and other postoperative complications was made between PV patients undergoing TKA and THA and their respective matched control groups.

Results: PV was significantly associated with increased rates of acute PE (2.3% vs 1.6%; odds ratio [OR] 1.44, 95% confidence interval [CI] 1.17-1.75), DVT (4.2% vs 3.6%; OR 1.40, 95% CI 1.20-1.61, $P < .001$), postoperative hematoma (0.6% vs 0.4%; OR 1.57, 95% CI 1.03-2.28), and SSI (4.5% vs 3.6%; OR 1.25, 95% CI 1.08-1.44, $P = .002$) following TKA. Among PV patients who underwent a primary THA, PV was significantly associated with increased rate of acute PE (1.9% vs 1.4%; OR 1.40, 95% CI 1.01-1.88, $P = .035$), DVT (3.5% vs 2.6%; OR 1.32, 95% CI 1.04-1.66, $P = .035$), postoperative hematoma (1.1% vs 0.6%; OR 1.86, 95% CI 1.22-2.80), and 1-year mortality (2.2% vs 1.6%; OR 1.43, 95% CI 1.06-1.89, $P = .016$).

Conclusion: PV was significantly associated with increased risk for DVT, PE, postoperative hematoma, SSI (TKA only), and 1-year mortality (THA only) following primary total joint arthroplasty.

The number of total knee arthroplasty (TKA) performed has risen dramatically in the last several years and projections indicate that, by 2050, the number of operations will increase by 855% [1]. In 2010, estimates concluded that there were approximately 2.5 million individuals with a total hip arthroplasty (THA), as compared to 4.7 million individuals with TKA [2]. Both THA and TKA have historically had favorable outcomes, and improve patient's quality of life.

Although successful, THAs and TKAs are not immune to complications. Orthopedic complications such as aseptic loosening, osteolysis, periprosthetic fracture, and heterotopic ossification are a few of the many implant-associated complications which can cause increased long-term hospital readmissions and revision surgery rates. However, it is often the nonorthopedic complications such as infection, myocardial infarction, and deep vein thrombosis (DVT) that increase acute global period resource utilization and mortality [3,4]. Without the use of venous thromboembolic (VTE) prophylaxis, the rate of DVT can be as high as 40%-85% following TKA and 40%-60% following THA [5]. This is significant given that VTE is associated with longer length of stay (LOS), cost, and mortality rate [6].

Polycythemia vera (PV) is a myeloproliferative disorder characterized by an overproduction of erythrocytes, leukocytes, and

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platelets and typically associated with a JAK2 V617F mutation [6]. Diagnosis is made by pan-elevation of the 3 cell lines, as well as a low erythropoietin level. Furthermore, PV patients are at an increased risk of developing second primary malignancies such as chronic myelogenous leukemia, further increasing morbidity and mortality in this patient population [7]. Although the prevalence of PV was only estimated to be 65,243 in 2003, modern medical treatment has increased the life expectancy of PV patients, and many patients with the disease are now candidates for joint replacement surgery [8]. PV could result in worse outcomes due to increased blood viscosity, resulting in increased risk for thromboembolic complications [8]. Furthermore, new evidence suggests that PV patients may also suffer from hemorrhagic complications, paradoxically [9–11]. Although these complications are documented in the general surgical population, there are minimal data regarding outcomes of primary joint arthroplasty among PV patients [12,13]. Other hematologic dyscrasias including coagulopathies, multiple myeloma, and chronic lymphocytic leukemia have demonstrated an increased risk of VTE following arthroplasty [14–17].

There are several other comorbid conditions that could confound PV's isolated effect on outcomes following THA and TKA [18–21]. As such, the aim of this investigation is to analyze outcomes following primary THA and TKA in PV patients while controlling for the comorbidities that could confound these results. We hypothesized that the presence of PV at the time of lower extremity arthroplasty would be associated with an increased risk of complications, most notably DVT and pulmonary embolism (PE).

Methods

Data Source

A retrospective database review of all Medicare patient records from 2005 to 2014 searchable by billable codes was performed utilizing the commercially available PearlDiver Patient Records Database (www.pearldiverinc.com; PearlDiver Inc, Colorado Springs, CO). As PearlDiver queried data are deidentified and Health Insurance Portability and Accountability Act compliant, this study was exempt from Institutional Review Board approval.

Study Population

All Medicare patients who underwent a primary TKA and THA from 2006 to 2013 were identified by querying the database separately for knee and hip procedures using International Classification of Diseases, Ninth Revision procedure codes 81.51 (THA) and 81.54 (TKA). Prior to the application of our exclusion criteria, the overall prevalence of PV among Medicare population undergoing a primary TKA and THA was queried. Exclusion criteria included age greater than 85 years old and malignancy or metastasis involving the hip or knee joint.

Following the application of our inclusion and exclusion criteria, the resulting cohort of primary total joint arthroplasty (TJA) patients was separated into patients with a prior history of PV (International Classification of Diseases, Ninth Revision, Clinical Modification: 2384; study group) and those without a prior diagnosis of PV (control group). Respective TKA and THA control groups were matched to identified PV patients based on the following demographic factors and comorbidities: age, gender, obesity, tobacco use history, alcohol abuse, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease, hyperlipidemia, and hypertension.

Postoperative Outcome Following Total Joint Arthroplasty Among Polycythemia Vera Patients

PV patients who underwent TKA and THA were compared to their respective matched control groups for hospital LOS, as well as the diagnosis of stroke, myocardial infarction, acute PE, acute lower extremity DVT, any incidence of postoperative allogeneic red blood cell or blood product transfusion, acute renal failure (ARF), septicemia, and hematoma within 90 days of joint replacement. Additionally, we compared both study groups and respective matched control groups for the postoperative diagnosis of postoperative infection including periprosthetic joint infection (PJI) and surgical site infections (SSIs), and mortality within 1 year of joint replacement.

Statistical Analysis

A Pearson's chi-squared analysis was used to assess differences in identified comorbidities and demographic factors as well as the

Table 1
Patient Demographics.

Total Numbers	TKA		*P*-Value	THA		*P*-Value
	Polycythemia Vera, 4643 (%)	Matched Control, 92,706 (%)		Polycythemia Vera, 2289 (%)	Matched Control, 45,622 (%)	
Age (y)						
<65	599 (12.9)	11,852 (12.8)	.937	342 (14.9)	6812 (14.9)	.994
65-69	930 (20.0)	18,269 (19.7)		418 (18.3)	8213 (18.0)	
70-74	1338 (28.8)	26,533 (28.6)		599 (26.2)	11,854 (26.0)	
75-79	1096 (23.6)	22,280 (24.0)		542 (23.7)	10,883 (23.9)	
80-84	680 (14.6)	13,772 (14.9)		388 (17.0)	7860 (17.2)	
Female gender	2095 (45.1)	41,870 (45.2)	.967	1223 (53.4)	24,370 (53.4)	1.000
Obesity (BMI >30 kg/m^2)	1027 (22.1)	20,436 (22.0)	.918	369 (16.1)	7340 (16.1)	.991
Tobacco use	1600 (34.5)	31,900 (34.4)	.956	915 (40.0)	18,156 (39.8)	.883
Alcohol abuse	169 (3.6)	3318 (3.6)	.859	114 (5.0)	2202 (4.8)	.776
Comorbidities						
Diabetes mellitus	1574 (33.9)	31,442 (33.9)	.996	716 (31.3)	14,247 (32.2)	.977
Peripheral vascular disease	484 (10.4)	9614 (10.4)	.926	242 (10.6)	4747 (10.4)	.825
Congestive heart failure	764 (16.5)	15,169 (16.4)	.884	383 (16.7)	7591 (16.6)	.930
COPD	1770 (38.1)	35,283 (38.1)	.944	920 (40.2)	18,309 (40.1)	.972
Hypertension	4001 (86.2)	79,902 (86.2)	.993	1919 (83.8)	38,272 (84.0)	.969
Hyperlipidemia	3432 (73.9)	68,546 (73.9)	.988	1656 (72.3)	33,037 (72.4)	.962

TKA, total knee arthroplasty; THA, total hip arthroplasty; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table 2
Postoperative Outcome of Primary Total Knee Arthroplasty in Polycythemia Vera Patients.

	PV, 4643 (%)	Matched Control, 92,706 (%)	*P*-Value	Adjusted OR (95% CI)	*P*-Value
Length of stay (d)	3.33 ± 2.05	3.30 ± 1.85	.325	–	–
90-d Stroke	104 (2.2)	2447 (2.6)	.106	0.86 (0.70-1.05)	.148
90-d Myocardial infection	51 (1.1)	939 (1.0)	.623	1.11 (0.82-1.45)	.487
90-d Acute pulmonary embolism	**107 (2.3)**	**1505 (1.6)**	**<.001**	**1.44 (1.17-1.75)**	**<.001**
90-d Deep vein thrombosis	**194 (4.2)**	**2828 (3.1)**	**<.001**	**1.40 (1.20-1.61)**	**<.001**
90-d Transfusion	83 (1.8)	2058 (2.2)	.056	0.80 (0.64-0.99)	.050
90-d Acute renal failure	85 (1.8)	1835 (2.0)	.511	0.93 (0.74-1.16)	.540
90-d Hematoma	**27 (0.6)**	**346 (0.4)**	**.034**	**1.57 (1.03-2.28)**	**.025**
90-d Septicemia	43 (0.9)	690 (0.7)	.190	1.26 (0.91-1.69)	.148
1-y Infection	**207 (4.5)**	**3344 (3.6)**	**.003**	**1.25 (1.08-1.44)**	**.002**
1-y Mortality	42 (0.9)	770 (0.8)	.647	1.08 (0.78-1.45)	.639

PV, polycythemia vera; OR, odds ratio; CI, confidence interval.
Bolded values are outcomes found to be significantly different between PV patients and matched controls.

differences in the rate of postoperative stroke, myocardial infarction, acute PE, DVT, ARF, septicemia, hematoma, infection, transfusion, and death. In addition, Welch's *t*-test was used to compare LOS between both groups. While controlling for all queried demographic factors and comorbidities as covariates, a multivariate logistic regression was used to analyze the independent effect of PV on postoperative outcomes following primary TKA and THA. R Project for Statistical Computing, available through the database, was used for all statistical analyses. Factors were considered significant at $P < .05$.

Results

Prevalence of PV in Medicare Population Undergoing Joint Replacement

The overall prevalence of PV within the queried Medicare population was 0.2%; 5410 patients out of 2,378,609 TKA patients had a prior diagnosis of PV. Likewise, the prevalence of PV among Medicare patients undergoing THA was 0.3%; 3085 patients had a diagnosis of PV before THA (1,143,523 patients).

Patient Demographics and Comorbidities

After the application of our inclusion and exclusion criteria, 4643 TKA and 2289 THA patients were identified that had a prior history of PV. There were no significant differences in demographic factors and comorbidities between each study group and respective control groups after matching (Table 1).

Postoperative Outcome Following Total Joint Arthroplasty Among Polycythemia Vera Patients

Total Knee Arthroplasty

Among primary TKA patients, PV was significantly associated with increased rate of acute PE (2.3% vs 1.6%; odds ratio [OR] 1.44, 95% confidence interval [CI] 1.17-1.75, $P < .001$), lower extremity DVT (4.2% vs 3.1%; OR 1.40, 95% CI 1.20-1.61, $P < .001$), and hematoma (0.6% vs 0.4%; OR 1.57, 95% CI 1.03-2.28, $P < .001$) within 90 days of TKA. PV was also independently associated with increased rate of postoperative infections (4.5% vs 3.6%; OR 1.25, 95% CI 1.08-1.44, $P < .002$) within 1 year of TKA. There were no differences found in the postoperative diagnosis of stroke (2.2% vs 2.6%; OR 0.86, 95% CI 0.70-1.05, $P = .148$), myocardial infarction (1.1% vs 1.0%; OR 1.11, 95% CI 0.82-1.45, $P = .487$), transfusion (1.8% vs 2.2%; OR 0.80, 95% CI 0.64-0.99, $P = .050$), ARF (1.8% vs 2.0%; OR 0.93, 95% CI 0.74-1.16, $P = .540$), and septicemia (0.9% vs 0.7%; OR 1.26, 95% CI 0.91-1.69, $P = .148$) between PV patients and the control group following TKA. There was no difference in LOS between both groups (3.33 142.05 vs 3.30 31.85, $P = .325$) (Table 2).

Total Hip Arthroplasty

PV was significantly associated with increased rate of acute PE (1.9% vs 1.4%; OR 1.40, 95% CI 1.01-1.88, $P < .035$), lower extremity DVT (3.5% vs 2.6%; OR 1.32, 95% CI 1.04-1.66, $P < .018$), and hematoma (1.1% vs 0.6%; OR 1.86, 95% CI 1.22-2.80, $P < .003$) within 90 days of THA. PV was also independently associated with increased mortality (2.2% vs 1.6%; OR 1.43, 95% CI 1.06-1.89, $P < .016$) within 1 year of THA. There were no significant differences found in LOS (3.62 ye2.43 vs 3.60 32.63, $P < .223$), postoperative stroke (3.1% vs 3.1%; OR 1.00, 95% CI 0.77-1.27, $P = .995$), myocardial infarction

Table 3
Postoperative Outcome of Primary Total Hip Arthroplasty in Polycythemia Vera Patients.

	PV, 2289 (%)	Matched Control, 45,622 (%)	*P*-Value	Adjusted OR (95% CI)	*P*-Value
Length of stay (d)	3.62 ± 2.43	3.60 ± 2.63	.223	–	–
90-d Stroke	70 (3.1)	1409 (3.1)	.984	1.00 (0.77-1.27)	.995
90-d Myocardial infection	21 (0.9)	603 (1.3)	.116	0.70 (0.44-1.06)	.116
90-d Acute pulmonary embolism	**43 (1.9)**	**621 (1.4)**	**.048**	**1.40 (1.01-1.88)**	**.035**
90-d Deep vein thrombosis	**79 (3.5)**	**1208 (2.6)**	**.024**	**1.32 (1.04-1.66)**	**.018**
90-d Transfusion	83 (3.6)	1561 (3.4)	.642	1.06 (0.84-1.32)	.605
90-d Acute renal failure	52 (2.3)	986 (2.2)	.779	1.08 (0.80-1.41)	.617
90-d Hematoma	**25 (1.1)**	**270 (0.6)**	**.004**	**1.86 (1.22-2.80)**	**.003**
90-d Septicemia	30 (1.3)	503 (1.1)	.410	1.21 (0.81-1.72)	.535
1-y Infection	75 (3.2)	1518 (3.3)	.942	0.98 (0.77-1.24)	.880
1-y Mortality	**51 (2.2)**	**713 (1.6)**	**.017**	**1.43 (1.06-1.89)**	**.016**

PV, polycythemia vera; OR, odds ratio; CI, confidence interval.
Bolded values are outcomes found to be significantly different between PV patients and matched controls.

(0.9% vs 1.3%; OR 0.70, 95% CI 0.44-106, $P = .116$), infection (3.2% vs 3.3%; OR 0.98, 95% CI 0.77-1.24, $P < .880$), transfusion (3.6% vs 3.4%; OR 1.06, 95% CI 0.84-1.32, $P = .605$), ARF (2.3% vs 2.2%; OR 1.08, 95% CI 0.80-1.41, $P = .617$), and septicemia (1.3% vs 1.1%; OR 1.21, 95% CI 0.81-1.72, $P = .535$) between PV patients and control group following THA (Table 3).

Discussion

Outcomes of primary TJA in patients with PV are not well known. Our study found that PV was independently associated with increased 90-day incidence of DVT, PE, and hematoma, as well as 1-year infection (both PJI and SSI) following TKA. Additionally, PV was significantly associated with increased 90-day incidence of DVT, PE, and hematoma, as well as 1-year mortality following THA. Of note, there was no significant difference in LOS, stroke, myocardial infarction, transfusion, ARF, and septicemia between our PV patients and the matched controls following both THA and TKA. Additionally, the present study reported the overall prevalence of PV among Medicare patients undergoing a primary TKA and THA to be 0.2% and 0.3%, respectively.

The prevalence of PV in the general population has been reported as 65,243 individuals, or 0.02% of the 2003 US population. The disparity between the prevalence of PV in literature and our reported prevalence is likely multifactorial. First, the average age that PV patients present for evaluation is 60 years; hence, the queried Medicare patients of age greater than 65 years will naturally contain a higher prevalence of PV as compared to the general US population [22]. Furthermore, PV patients undergo more joint arthroplasties as a result of increased incidence of arthropathies such as gouty arthritis from high cell turnover and hyperuricemia.

The pathogenesis responsible for PV patients' worsened outcome following primary THA and TKA is attributed to thrombus formation from increased blood viscosity secondary to erythrocytosis from a JAK2 mutation. Factors including increased hematocrit and thrombocytosis have also been implicated in the association between PV and thrombosis [23]. Additionally, it is known that surgery itself causes the induction of the coagulation cascade and further activation of thrombogenic factors via endothelial injury and venous stasis [24]. Similarly, blood loss from the procedures can inhibit the fibrinolytic system and therefore promote thrombus formation, though this is a rare complication associated with most surgeries including THA and TKA [25,26]. Paradoxically, there are case reports that demonstrate that PV can lead to hemorrhage [9–11].

The results of this study align well with the current literature on PV and associated hematologic neoplasms and their effects on outcomes following TKA and THA. Studies on other hematologic malignancies, including multiple myeloma and leukemia, found an increase in VTE following joint arthroplasty [12,23]. Another study that evaluated postoperative outcome of PV patients following nonspecific surgical procedures found that VTE events, vascular occlusion, and hemorrhage were more frequent among PV patients as compared to controls, which aligns with our findings [27]. In a study by Newman et al [19] on the effects of various hematologic malignancies including myeloproliferative neoplasms on outcome following THA, myeloproliferative neoplasms were associated with a significant increase in the rate of hematoma. Conversely, myeloproliferative neoplasms were insignificantly associated with an increase in DVT, PE, and infection following THA [19]. Nonetheless, our results show that the rate of VTE was significantly higher among PV patients compared to matched controls following THA.

Similar studies have been performed that evaluated the effect of hematologic malignancies on outcomes following TKA and concluded that myeloproliferative disease was associated with an increased risk of DVT and hematoma, but not PE or infection [20]. Conversely, our findings indicated that PE and infection, in addition to DVT and hematoma, were significantly higher in the PV cohort than the matched controls. In both THA and TKA, it has been hypothesized that the counterintuitively increased risk of hematoma in myeloproliferative patients was due to developing bleeding diathesis. Surprisingly, while the rate of hematoma was significant between PV and matched controls following THA and TKA, the rate of transfusions was not, which contrasts with the results of other studies [28]. It is likely that the development of hematomas following THA and TKA in the present study was not significant enough to warrant a transfusion, but significant enough to be coded as a hematoma. Recent guidelines recommend the use of cytoreductive therapy in high risk patients, low dose aspirin, and standard anticoagulation protocols as prophylaxis for PV patients in addition to indefinite anticoagulation among patients with a history of unprovoked VTE [29,30]. Considering these findings, PV patients undergoing TJA should continue with standard VTE prophylaxis in addition to increased close monitoring, especially in the early postoperative period.

Although our study found no difference in ARF among PV patients, significant differences in rates of ARF following THA in myeloproliferative patients have been documented in the literature [19]. In terms of TKA, our study found no difference in the rate of ARF among PV patients, in agreement with prior research [20]. These differences are likely due to the lack of stratification within myeloproliferative disorders in other studies. Although PV and other myeloproliferative disorders share a common theme of increased proliferation, myelofibrosis has a more significant impact on renal function as compared to PV [31]. Nonetheless, PV patients undergoing TJA would benefit from continued aggressive monitoring of renal parameters, and adequate hydration to enhance renal perfusion postoperatively.

Our study found a significant increase in 1-year infection risk following TKA, though, surprisingly there was no difference in 1-year infection risk following THA. Although there are no studies that have examined infection risk among PV patients following orthopedic surgeries, studies that have monitored postoperative outcome of patients with malignancy following TJA reported an increased risk of PJI [32]. Additionally, the risk of PJI is modestly higher following knee arthroplasty than hip, which could have contributed to the increased risk following TKA but no added risk following THA [33]. Furthermore, our study found no significant difference in the 90-day risk of septicemia following joint arthroplasty. There are no studies that investigated the risk of septicemia following TJA in PV patients. However, one study concluded that the risk of septicemia was higher in multiple myeloma patients following hip surgery, though this was likely due to the loss of immunoglobulins which PV patients do not suffer from [34]. The lack of an association between septicemia and PV following THA and TKA is likely corroborated by the already low (1 in 300) incidence of septicemia following joint arthroplasty in healthy patients [35,36].

Given the scarcity of literature on PV patients' outcomes following TKA and THA, this study has much strength. To our knowledge, it is the first study to investigate the effect of PV on outcomes and complications following TKA and THA. Additionally, its large sample size, despite the relatively low prevalence of PV, further adds to this study's ability to draw generalizable conclusions regarding PV's effect on outcome following TKA and THA. This study also controlled for confounding comorbid conditions that could have influenced outcome following TJA. Finally, our study has longer follow-up data compared to other national database studies; other studies of similar size and content only evaluated complications, infection, and mortality during the LOS and not after discharge [18,19].

The present study has a few limitations. The data used in this study were obtained from a Medicare database and therefore rely on the accuracy of data entry into the electronic health record [31]. Errors in the coding of comorbidities have been reported which can potentially skew our results [32]. Unlike Newman et al, this study did not analyze differences in cost between PV and matched control patients [18,19]. If performed, this study would have driven greater insight into total cost associated with the care of PV patients. Additionally, the database used in the present study does not account for differences in postoperative management between PV patients and controls. For instance, the methodology did not account for differences in postoperative anticoagulation prophylaxis or PV treatment modalities that could affect evaluated outcomes.

Conclusions

As TKA and THA operations continue to rise, PV will be an increasingly common comorbidity that will require altered preoperative planning and postoperative patient care. As expected, PV was significantly associated with DVT and PE following primary TJA. PV was also associated with hematoma following TJA. Finally, PV patients undergoing TKA had an increased risk for SSI, and those undergoing THA had increased 1-year mortality, postoperatively.

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