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Original Article

Impact of chronic thrombocytopenia on healthcare resource utilization, in-hospital outcomes, and costs following percutaneous coronary intervention of chronic total occlusion: a nationwide propensity weighted analysis

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Abstract: Background: Data on the impact of chronic thrombocytopenia (CT) on outcomes following chronic total occlusion (CTO) percutaneous coronary interventions (PCI) is limited. Most studies are case reports and focused on postprocedural thrombocytopenia. The purpose of this present study is to assess the impact of CT (> one year) on health resource utilization (HRU), in-hospital outcomes, and cost following CTO PCI. Methods: We used discharge data from the 2016-2018 National Inpatient Sample and propensity score-weighted approach to examine the association between CT and HRU among patients undergoing CTO PCI. HRU was measured as a binary indicator defined as a length of stay greater than seven days and/or discharge to a non-home setting. The cost was measured as total charges standardized to 2018 dollars. Both outcomes were assessed using generalized linear models adjusted for survey year, and baseline characteristics. Results: Relative to its absence, the presence of CT following CTO PCI was associated with a 4.8% increased probability of high HRU (Population Average Treatment Effect (PATE) estimate = 0.048; 95% Confidence Interval (CI) = 0.041-0.055; P<0.001) and approximately $18,000 more in total hospital charges (PATE estimate = +$18,297.98; 95% CI = $15,101.33-$21,494.63, P<0.001). Conclusion: Among chronic total occlusion patients undergoing percutaneous coronary intervention, those with chronic thrombocytopenia had higher resource use, including total hospital charges, and worse in-hospital outcomes when compared with those without chronic thrombocytopenia.

Keywords: Chronic total occlusion, healthcare resource utilization, percutaneous coronary intervention

Introduction

Several inflammatory modulators are implicated in the pathogenesis of coronary artery disease. Platelets are vital in the cascade of events leading to acute coronary syndrome [1, 2]. Platelet inhibition is the current therapeutic paradigm for acute coronary syndrome, including percutaneous coronary intervention (PCI) [3]. Practice guidelines advocate for dual antiplatelet therapy following revascularization of diseased coronary vessels using drug-eluting stents [4]. However, this antiplatelet strategy is associated with an increased risk of bleeding [5], especially for those with chronic thrombocytopenia (CT) [6]. Chronic total occlusion (CTO) of a coronary artery is 100% occlusion of its lumen over a period of more than 120 days (about four

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months) with concomitant Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow (true occlusion) or a TIMI grade 1 flow (functional occlusion) [7].

Approximately 15% of patients with CTO of a coronary artery present with unstable angina; others experience chronic stable angina, while most of these patients may be asymptomatic [8]. Patients who remain symptomatic despite maximally tolerated guideline-directed medical therapy may opt for revascularization with PCI using drug-eluting stents [8]. There is a lack of consensus strategy in managing patients with CT. Unfortunately, patients with CT have invariably been excluded from randomized clinical trials of CTO PCI or secondary prevention antithrombotic therapies [9]. Ayoub et al. evaluated the clinical impact of CT on in-hospital outcomes following PCI. They found that patients undergoing PCI with CT had a doubled risk of post-procedural bleeding, a higher risk of post-procedural vascular complications, and higher in-hospital mortality when compared to those without CT [10]. This pivotal study included all PCI patients irrespective of their indication for this revascularization strategy. Unfortunately, data on the clinical impact of CT following PCI in CTO patients is lacking. To help fill this void in the appreciation of the safety of PCI in this under-studied CTO population, we hypothesized that chronic thrombocytopenia portends adverse clinical outcomes, including high resource utilization (HRU) and costs in CTO patients when compared to those without thrombocytopenia, using a large all-payer inpatient database.

Methods

Data source

The National Inpatient Sample (NIS) is a publicly accessible database of all-payer discharge data maintained under the auspices of the Agency for Healthcare Research and Quality (AHRQ). The NIS comprises patient-level and hospital-level data from about 8 million hospitalizations and a proportionate sample of 20% of community healthcare facilities in the United States. The NIS sampling methodology allows for applying weights to variables to obtain annual national estimates. NIS has been validated against several hospital-level databases in the United States [11, 12].

Study selection, endpoints, and definitions

The authors queried patient-level and hospital-level discharge data from the NIS database between 2016 and 2018 with a primary or secondary diagnosis of CT, during which PCI was performed on account of CTO (ICD-10-CM codes D696, D6949, D6942, D693, D694, and D6959). CT is a blood platelet count of less than 150,000 cells/μl. In the NIS, the CT diagnosis is exacted based on these ICD 10 codes without the exact laboratory values. To select study subjects with CT, we used a chronic indicative variable, which isolated the diagnosis of interest CT that was present at least 12 months from the index hospitalization. The Patients with acute thrombocytopenia in whom or for whom the chronic indicative variable showed that the diagnosis of interest was present for less than 12 months from the index admission were excluded. Those with periprocedural thrombocytopenia, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulopathy were also excluded.

The primary outcome of interest was HRU, a binary indicator defined as a length of stay greater than seven days or discharge to a non-home setting [13, 14]. Secondary endpoints were In-hospital mortality, vascular complication, mechanical circulatory support, stroke, permanent pacemaker placement (PPM), acute kidney injury (AKI), dialysis, and cost. Cost was adjudicated as total charges obtained from the NIS data standardized to the dollar's value in 2018. These diagnoses were obtained in parallel, as both International Classification of Diseases-10th Edition-Clinical Modification (ICD-10-CM) and clinically meaningful clusters of ICD-10-CM codes, termed Clinical Classification Software codes. Given that the NIS database contained de-identified patient clinical data, the study was exempt from Institutional Review Board approval.

Statistical analysis

We applied weights provided by the NIS to obtain actual annualized estimates of admissions during the study period. To account for the complex sampling of the NIS, we followed the propensity score weighting approach for data as outlined by DuGoff and colleagues [15]. Propensity scores were calculated by estimat-

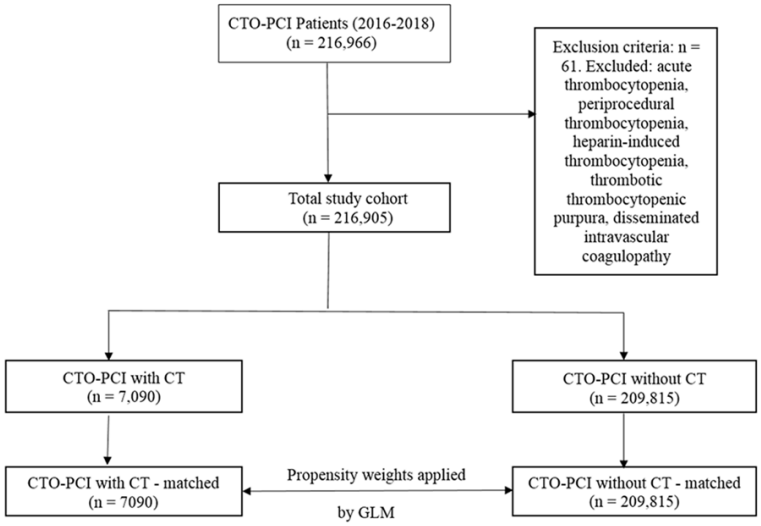

Figure 1. Study flowchart showing inclusion and exclusion criteria utilized in recruiting the study population. CTO, chronic total occlusion; CT, chronic thrombocytopenia; PCI, percutaneous coronary intervention; GLM, generalized linear model.

ing the probability of having CT as a function of patient-level and hospital-level covariates. The effect of CT on HRU among patients undergoing CTO PCI was then assessed using generalized linear models (GLM) weighted by a combined weight derived from the propensity score and survey weights. HRU was evaluated using a GLM model with binomial distribution and a log link. A GLM model with gamma distribution and a log link was also used to assess total charges. GLM models were also adjusted for the survey year, illness severity, and all the covariates. All analyses were completed in Stata v.17, incorporating primary sampling units and clusters to obtain national estimates. Statistical significance was assessed at P<0.05 using two-tailed tests.

Results

Baseline characteristics and matched cohorts

Two hundred sixteen thousand nine hundred sixty-six (216,966) patients underwent PCI due to CTO during the study duration of 2016 to 2018 (**Figure 1**). After excluding patients with acute thrombocytopenia, periprocedural thrombocytopenia, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation, 216,905 patients were identified and included in the study. CT was present in 7090 patients (3.3%). Before propensity score weighting, the CT and non-CT groups differed regarding all assessed patient and hospital-level characteristics. Specifically, patients with CT were older (69.2 years vs. 65.1 years; P<0.001), were considered to have a more clinically severe illness (average illness severity score of 3.2 vs. 2.2; P<0.001) and were more likely to have two or more comorbidities (85.1% vs. 66.0%; P<0.001). Patients with CT were also more likely to be male (71.6 vs. 66.0%; P<0.001) and less likely to be Black (9.0% vs. 9.7%; P<0.01). They were more likely to have public insurance (76.3% vs. 64.5%; P<0.001) and reside in a metropolitan area (83.1% vs. 81.2%; P<0.001), but less likely to have received care at small (12.1% vs. 14.5%; P<0.001), rural hospitals (3.9% vs. 5.5%; P<0.001), and hospitals located in the Northeast region (15.4% vs. 18.0%; P<0.001). They were, however, more likely to be cared for in private non-profit hospital facilities (76.7% vs. 74.9%; P<0.01). The application of propensity score weights balanced the two groups regarding all assessed patient-level and hospital-level covariates (**Table 1**).

Predictors of high resource utilization and total charges

CT during CTO PCI was associated with a higher likelihood of high resource use (b = 0.212; 95% CI = 0.191-0.235; P<0.001). Relative to its absence, CT during CTO PCI was associated with an approximately 6.97% increased probability of high resource use (Population Average Treatment Effect (PATE) estimate = 0.0697; 95% Confidence Interval (CI) = 0.0617-0.0776; P<0.001). Patient-level characteristics that independently predicted HRU included female sex compared to male (b = 0.070; 95% CI = 0.044-0.097; P<0.001); the other race categories (racial minorities) compared to Non-Hispanic White (b = 0.048; 95% CI = 0.007-0.089; P = 0.023); public insurance coverage, compared to self-pay or uninsured (b = 0.187;

Table 1. Baseline demographic and clinical characteristics of CTO PCI with and without CT before and after application of Propensity weights

Variables	Before Application of Propensity Weights			After Application of Propensity Weights		
	CTO-PCI with CT (n = 7090)	CTO-PCI without CT (n = 209,815)		CTO-PCI with CT (n = 7090)	CTO-PCI without CT (n = 209,815)	
	Mean (standard error)	Mean (standard error)	*P* value	Mean (standard error)	Mean (standard error)	*P* value
Illness Severity Index	3.18 (0.009)	2.22 (0.003)	<0.0001	3.06 (0.012)	3.03 (0.013)	0.456
	%	%	*P* value	%	%	*P* value
Sex			<0.0001			0.8989
Female	28.4	34.0		33.9	33.8	
Male	71.6	66.0		66.1	66.2	
Age			<0.0001			0.3334
18-44 years	2.4	5.1		5.2	5.0	
45-64 years	31.2	42.6		41.0	42.3	
65 years and above	66.3	52.3		53.7	52.7	
Race/Ethnicity			0.0060			0.9700
White	74.8	75.4		75.6	75.4	
Black	9.0	9.7		9.5	9.7	
Hispanic	8.8	8.3		8.3	8.3	
Others (Pacific islander, Native Americans, Asians)	7.5	6.6		6.7	6.7	
Comorbidity						
Diabetes Mellitus	46.7	39.6	<0.001	45.9	46.9	0.27
Chronic kidney disease	31.3	14.4	<0.001	30.5	31.8	0.12
Coronary artery disease	95.0	94.7	0.16	95.3	95.6	0.42
Congestive heart failure	39.9	20.6	<0.001	38.9	39.7	0.37
Atrial fibrillation	23.2	11.7	<0.001	22.1	21.7	0.55
Grouped Charlson comorbidity index			<0.0001			0.974
0	1.8	5.0		4.9	4.9	
1	13.1	29.0		28.3	28.5	
2	85.1	66.0		66.8	66.6	
Patient Location of Residence			0.0002			0.378
Metro	83.1	81.2		81.8	81.3	
Non-metro	16.9	18.8		18.2	18.7	
Insurance type			<0.0001			0.8916
Public	76.3	64.5		65.2	64.9	
Private	20.7	30.5		29.8	30.2	
Uninsured	3.1	5.0		4.9	5.0	

Hospital Region			<0.0001			0.804
Northeast	15.4	18.0		18.4	17.9	
Midwest	23.8	22.4		22.1	22.4	
South	41.6	42.4		42.4	42.4	
West	19.2	17.3		17.1	17.3	
Hospital Bed size			<0.0001			0.8109
Small	12.1	14.5		14.7	14.4	
Medium	29.1	29.8		29.9	29.8	
Large	58.8	55.7		55.4	55.8	
Hospital type			<0.0001			0.8490
Rural	3.9	5.5		5.3	5.5	
Urban non-teaching	21.5	23.4		23.5	23.3	
Urban teaching	74.6	71.1		71.3	71.2	
Hospital Control			0.0059			0.7542
Government	7.8	8.7		9.0	8.7	
Not-for-profit	76.7	74.9		74.9	75.0	
For profit	15.6	16.4		16.1	16.4	

Abbreviations: CT, chronic thrombocytopenia; CTO, chronic total occlusion; PCI, percutaneous coronary intervention; US, United States. Data presented as mean + standard deviation or n (%).

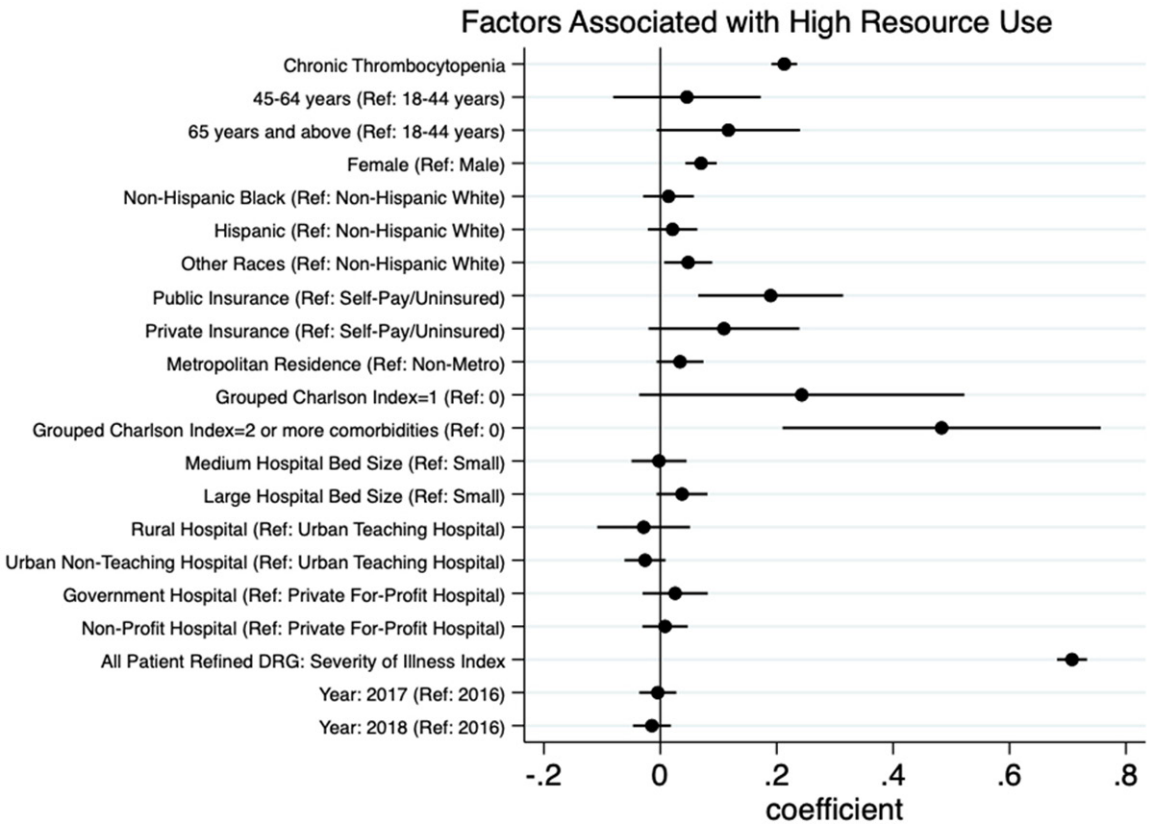

Figure 2. Forest plot illustrating the patient level and clinical factors that independently predicted HRU. Abbreviations: AKI, acute kidney injury; CTO, chronic total occlusion; DM, diabetes mellitus; HRU, High Resource utilization; PCI, percutaneous coronary intervention; PPM, permanent pacemaker. Data presented as mean + standard deviation, median (IQR), or n (%).

95% CI = 0.062-0.313; P = 0.003); the presence of 2 or more comorbidities compared to none (b = 0.483; 95% CI = 0.2109-0.757; P = 0.001); and high illness severity index (b = 0.707; 95% CI = 0.682-0.733; P<0.001) (**Figure 2**).

In the adjusted GLM model, the presence of CT during CTO PCI was associated with higher procedural cost (*b* = 0.129; 95% Confidence Interval (CI) = 0.107-0.151; P<0.001). Relative to its absence, CT during CTO PCI was associated with approximately $18,000 more in total hospital charges (Population Average Treatment Effect (PATE) estimate = +$18,297.98; 95% CI = $15,101.33-$21,494.63, P<0.001).

Patient-level characteristics associated with total charges included race, residence, and illness severity. Compared to non-Hispanic whites, Non-Hispanic Blacks were associated with lower total charges (*b* = -0.059; 95% CI = -0.096-0.022; P = 0.002). In contrast, Hispanic (*b* = 0.123; 95% CI = 0.078-0.168; P<0.001), and other races (*b* = 0.076; 95% CI = 0.028-0.123; P = 0.002) were associated with higher total charges, relative to Non-Hispanic Whites. Total charges were also higher for patients in metropolitan areas than non-metropolitan areas (*b* = 0.077; 95% CI = 0.044-0.110; P<0.001). Illness severity was also associated with higher total charge (*b* = 0.381; 95% CI = 0.367-0.395; P<0.001).

Hospital-level factors associated with higher total charges included a location in the West region, compared to the Northeast (*b* = 0.211; 95% CI = 0.147-0.274; P<0.001), and medium (*b* = 0.120; 95% CI = 0.073-0.166; P<0.001) and larger (*b* = 0.172; 95% CI = 0.128-0.216; P<0.001) bed size, compared to small bed size. On the other hand, total charges were lower in the Midwest, compared to the Northeast (*b* = -0.112; 95% CI = -0.167--0.056; P<0.001) and

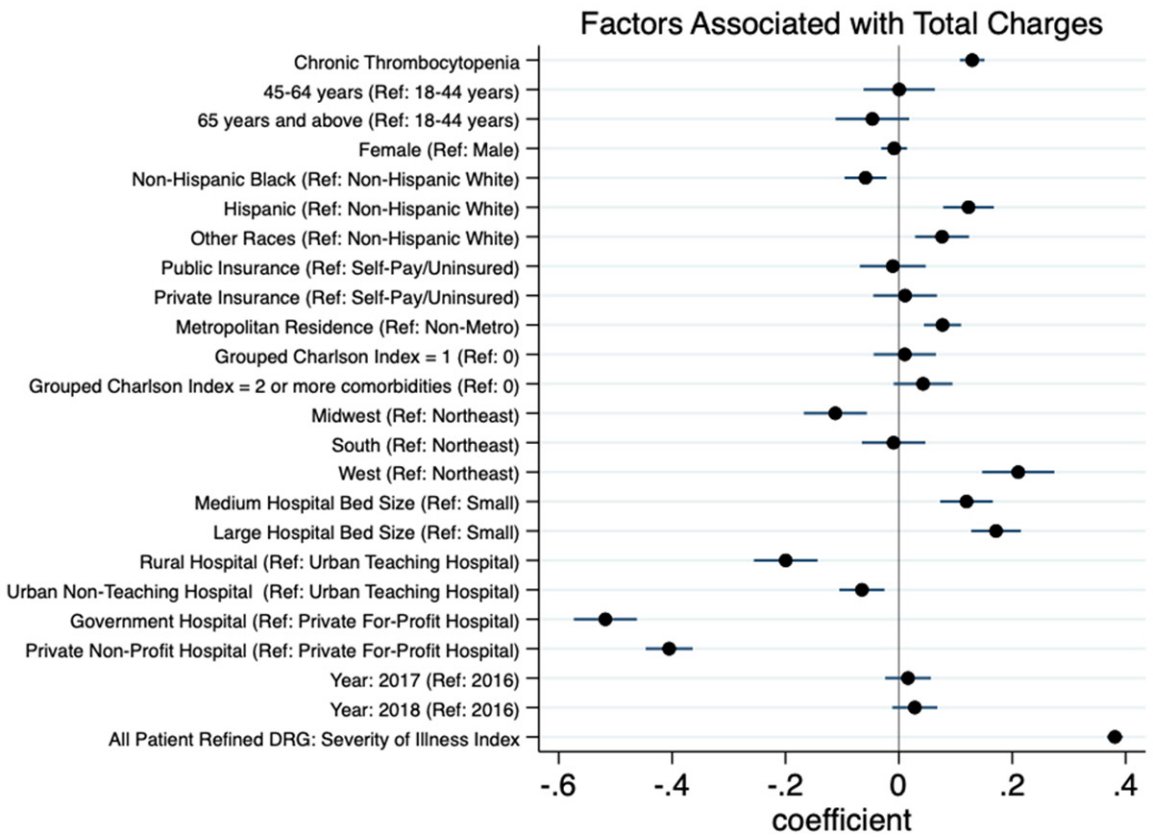

Figure 3. Forest plot illustrating the patient level and clinical factors that independently predicted total charges. Abbreviations: AKI, acute kidney injury; CTO, chronic total occlusion; DM, diabetes mellitus; HRU, high resource utilization; PCI, percutaneous coronary intervention; PPM, permanent pacemaker. Data presented as mean + standard deviation, median (IQR), or n (%).

in government (*b* = -0.517; 95% CI = -0.573--0.462; P<0.001) and private non-profit (*b* = -0.405; 95% CI = -0.447--0.364; P<0.001), compared to for-profit hospitals. Total charges were also lower in rural (*b* = -0.200; 95% CI = -0.256--0.144; P<0.001) and urban non-teaching hospitals (*b* = -0.065; 95% CI = -0.105--0.026; P = 0.001), compared with urban teaching hospitals (**Figure 3**).

Periprocedural complications and clinical outcomes

Before applying propensity weights, CTO-PCI with CT patients had higher in-hospital mortality when compared to the CTO-PCI without CT patients (9.13% vs. 2.50%, P<0.001). Vascular complication was higher in the CTO-PCI patients (2.12%, P<0.001), while that in the CTO-PCI without CT patient was 0.91%, P<0.001. There was higher use of mechanical circulatory support in the CTO-PCI with CT group compared to the CTO-PCI without CT group (5.29% vs. 1.07%, P<0.001). Placement of permanent pacemakers was higher in the CTO-PCI with CT group, compared to the CTO-PCI without CT group (1.51 vs. 0.52%, P<0.001). Acute kidney injury (AKI) was 35.18% (P<0.001) in the CTO-PCI with CT cohort, while the AKI rate in the CTO-PCI without CT cohort was 13.84% (P<0.001). The use of dialysis, in terms of weight percentage, was 4.47% (P<0.001) in the CTO-PCI with CT cohort, while in the CTO-PCI without CT group, it was 1.29% (P<0.001). There was no difference in stroke rate between the two groups, **Table 2**.

Following the application of propensity score weights as shown in **Table 3**, CT was more likely to be associated with In-hospital mortality in subjects following CTO PCI compared to those without CT, with population average treatment effect (PATE) of 1.02, P<0.001. CT was associated with high use of mechanical circulatory

Table 2. In-hospital outcomes of study population stratified by CT status before application of propensity weights

Variable	CTO-PCI with CT (n = 7090) Weighted %	CTO-PCI without CT (n = 209,815) Weighted %	*P*-value
In hospital mortality	9.13	2.50	<0.001
Vascular complication	2.12	0.91	<0.001
Mechanical Circulatory Support	5.29	1.07	<0.001
Stroke	0.12	>0.01	0.3940
PPM placement	1.51	0.52	<0.001
AKI	35.18	13.84	<0.001
Dialysis	4.47	1.29	<0.001

Table 3. Association between chronic thrombocytopenia and in-hospital outcomes among patients undergoing PCI following propensity score weighting

Outcomes	PATE (Percentage point difference)	95 Confidence Interval	*P*-value
In-Hospital Mortality	1.03	0.61-1.45	<0.001
Vascular Complication	0.25	-0.02-0.51	0.0677
Mechanical Circulatory support	1.31	0.99-1.64	<0.001
Stroke	-0.12	-0.17–0.07	<0.001
PPM Placement	0.98	0.64-1.31	<0.001

Note: Reported PATE represents the average difference in the predicted probability of outcomes for CT and non-CT patients nationally. Each in-hospital outcome was modeled using a GLM with binomial distribution and a log link. Each model adjusted for all covariates listed in **Table 1**, including survey year and illness severity index.

support following CTO PCI with a population average treatment effect (PATE) of 1.31, P<0.001. CT was also associated with a higher placement of permanent pacemakers compared with those without CT following CTO PCI with a population average treatment effect (PATE) of 0.98, P<0.001.

Discussion

Major findings

The significant findings of this analysis of CTO patients following PCI are as follows: 1. Chronic thrombocytopenia was associated with high healthcare resource utilization, adjudicated as prolonged length of stay greater or equal to 7, or discharge to non-home settings following CTO PCI. 2. Chronic thrombocytopenia was associated with increased hospitalization costs, the surrogate of total charges standardized to the value of the dollar in 2018 when compared to patients without chronic thrombocytopenia. 3. Chronic thrombocytopenia was predictive of adverse clinical outcomes, including in-hospital mortality and peri-procedural complications, compared to those without chronic thrombocytopenia.

CTO PCI is a complex and high-risk procedure in patients with inherent high bleeding risks, such as those with chronic thrombocytopenia. The current practice guideline recommends a balanced consideration of bleeding with ischemic risks in these high-risk patients [16]. Unfortunately, patients with chronic thrombocytopenia are mostly excluded from most randomized controlled clinical trials, including Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) trial, the Platelet inhibition, and patient Outcomes (PLATO) trial, the cangrelor versus standard therapy to achieve optimal Management of Platelet Inhibition (CHAMPION) trials [17-19]. Ayoub K et al. recently showed in a large retrospective propensity analysis that patients with CT were at higher risk of hospitalization, including a higher risk of in-hospital mortality [10]. Impact of chronic thrombocytopenia on healthcare resource utilization and cost is lacking. The current study addresses this critical question in a large, propensity-weighted analysis of CTO patients following PCI.

Chronic thrombocytopenia was as high as 3.3% in all patients undergoing CTO PCI. This is slightly higher than the incidence in Denmark, Sweden, and Norway [20], underscoring the

need to assess the impact of this common entity, chronic thrombocytopenia, on healthcare resource utilization and cost while optimizing care for CTO patients undergoing PCI.

The clinical benefits of CTO revascularization by PCI are inconsistent. In a recent large meta-analysis, Khan et al. reported lower long-term mortality and cardiac deaths in the CTO-PCI group compared to OMT. However, this apparent clinical benefit was driven by the recruited observational studies, while the included randomized control trials (RCT) showed no significant differences in major adverse cardiac events, including myocardial reinfarction, stroke, or repeat PCI [21]. The plausible explanation for this inconsistency of the benefits of these CTO RCTs is related to the low enrollment number of CTO patients, resulting in the trials being underpowered to show any benefit PCI [22-25]. There was also a high crossover rate exacting selection bias [22-25].

Despite these inconsistencies in clinical benefits as demonstrated by these CTO RCTs, expert consensus guideline recommends CTO PCI for symptomatic relief of angina [26]. Therefore, in CTO patients with Chronic thrombocytopenia, in whom there may be a likelihood of adverse events, there is a need to carefully select patients whose revascularization is likely to provide symptomatic relief while mitigating bleeding. In this analysis utilizing propensity weights, patient and hospital-level variables were homogenously distributed between the cohort with CT and the group without CT following CTO PCI. One important variable that may have contributed to the adverse events, including high resource utilization, costs, and other clinical outcomes, including in-hospital mortality observed in the CTO-PCI with CT group, maybe operator-dependent variables, including techniques and skill, which is not available in an administrative database like the NIS.

Operator-dependent variables that may affect clinical outcomes may include the use of microcatheter to optimize exchanges and guidewire manipulation [26, 27], antegrade wiring, antegrade dissection and reentry [28], and the retrograde approach [28]. Intracoronary imaging may also mitigate the risk of adverse events [29-32], including healthcare resource utilization, costs, and in-hospital mortality. RCTs testing these operator-dependent variables are desperately needed.

Limitations

This study, like all retrospective observational analyses, has limitations. These limitations help put the study's findings and conclusions into perspective in generalizability to other populations. The NIS is an administrative database subject to the effect of measured and unmeasured confounders. Statistical methods such as propensity-matching tools eliminated most of these confounders. Despite these propensity-matching techniques utilized in this study, we could not eliminate the effect of unmeasured confounders that might have contributed to this study's reported results and findings.

Secondly, we could not stratify the analysis based on the severity of CT. The granular data points, including laboratory results, are unavailable in the NIS database. Hence, studies such as this one, whose findings are based on ICD-10-CM codes, can be challenging. Third, the NIS database was prepared by trained coding specialists after reviewing inpatient-level and hospital-level records for both reporting and reimbursement purposes by the Center for Medicare and Medicaid Services. Therefore, the data are subject to potential oversights in documentation and coding in preparing this nationwide registry. However, NIS may be plagued by coding errors. Despite these limitations, the large number of patients studied provides valuable data in this under-studied thrombocytopenic CTO population following PCI.

Conclusion

In this propensity-weight analysis of patients undergoing chronic total occlusion percutaneous coronary intervention, patients with CT are at higher risk of high resource utilization, worse clinical outcomes, and higher costs when compared to those without CT, within the confines of the limitations of this retrospective study. High-fidelity studies are needed to validate these findings and elucidate strategies to mitigate adverse outcomes in this population.

Disclosure of conflict of interest

None.

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