Venous Thromboembolism following Microsurgical Breast Reconstruction: A Longitudinal Analysis of 12,778 Patients

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PATIENT SAFETY

RISK

Background: Venous thromboembolism is a dreaded complication following microsurgical breast reconstruction. Although the high-risk nature of the procedure is well known, a thorough analysis of modifiable risk factors has not been performed. The purpose of this study was to analyze the association of such factors with the postoperative occurrence of venous thromboembolism longitudinally.
Methods: Using the Truven MarketScan Database, a retrospective cohort study of women who underwent microsurgical breast reconstruction from 2007 to 2015 and who developed postoperative venous thromboembolism within 90 days of reconstruction was performed. Predictor variables included age, timing of reconstruction, body mass index, history of radiation therapy, history of venous thromboembolism, Elixhauser Comorbidity Index, and length of stay. Univariate analyses were performed, in addition to logistic and zero-inflated Poisson regressions, to evaluate predictors of venous thromboembolism and changes in venous thromboembolism over the study period, respectively.
Results: Twelve thousand seven hundred seventy-eight women were identified, of which 167 (1.3 percent) developed venous thromboembolism. The majority of venous thromboembolisms (67.1 percent) occurred following discharge, with no significant change from 2007 to 2015. Significant predictors of venous thromboembolism included Elixhauser score ($p < 0.01$), history of venous thromboembolism ($p < 0.03$), and length of stay ($p < 0.001$). Compared to patients who developed a venous thromboembolism during the inpatient stay, patients who developed a postdischarge venous thromboembolism had a lower mean Elixhauser score ($p < 0.001$).
Conclusions: Postoperative venous thromboembolism continues to be an inadequately addressed problem, as evidenced by a stable incidence over the study period. Identification of modifiable risk factors, such as length of stay, provides potential avenues for intervention. As the majority of venous thromboembolisms occur following discharge, future studies are warranted to investigate the role for an intervention in this period. (*Plast. Reconstr. Surg.* 146: 465, 2020.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Prevention of venous thromboembolism has become a leading priority in plastic surgery. Venous thromboembolism events, which encompass both deep venous thrombosis and

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pulmonary embolism, contribute to over 100,000 deaths annually in the United States[1] and generate a $7 to $10 billion annual cost to the U.S. health care system.[2] An estimated 40 to 80 percent of surgical cancer patients will develop a deep venous thrombosis without preventive measures, and pulmonary embolism is the leading serious complication among hospitalized surgical patients.[3] Recognizing the significant morbidity and mortality associated with this disease, several leading organizations in plastic surgery have formed initiatives with the objective of reducing venous thromboembolism events, such as the American Society of Plastic Surgeons Venous Thromboembolism Task Force, the Plastic Surgery Foundation–funded Venous Thromboembolism Prevention Study, and an American Association of Plastic Surgeons–sponsored consensus conference.[4–7]

Current recommendations from the American Association of Plastic Surgeons–sponsored panel call for consideration of chemoprophylaxis in high-risk plastic surgery patients, defined as those with a 2005 Caprini Risk Assessment Model score of greater than 8.[4] These recommendations are largely formulated based on a systematic review of relevant literature in adjacent specialties and plastic surgery, such as the Venous Thromboembolism Prevention Study,[6–8] rather than by applying evidence of venous thromboembolism risk reduction in patients undergoing abdominal and pelvic surgery.[9,10] Challenges facing such scholarly efforts in plastic surgery include the general lower risk profile of the average plastic surgery patient.[7] In addition, the optimal duration of chemoprophylaxis is unknown, because the Venous Thromboembolism Prevention Study protocol called for a constant chemoprophylactic regimen limited to inpatient stay.[4]

With over 19,000 annual cases in 2017, autologous breast reconstruction represents nearly 19 percent of postmastectomy breast reconstructions in the United States and introduces a large pool of women into the at-risk stratum for venous thromboembolism.[11] The incidence of venous thromboembolism in these patients, who generally have a high baseline preoperative risk because of active malignancy, age older than 40 years, and higher body mass index, remains unclear.[3,12] Symptomatic venous thromboembolism rates of up to 6.7 percent have been reported for women undergoing autologous breast reconstruction,[13] and published rates of asymptomatic venous thromboembolism are as high as 20.4 percent.[14] However, these and other existing studies are limited in breadth and impact because of confinement to one or two institutions and consequent restricted sample size.[12–16] The objectives of this study were to (1) determine the distribution over time of venous thromboembolism events after free autologous breast reconstruction, and (2) analyze associations with patient and modifiable risk factors to target for risk reduction.

PATIENTS AND METHODS

Database

We performed a retrospective cohort study using deidentified data from the Truven MarketScan databases, which collectively contain health care data on nearly 240 million covered lives from more than 32 billion service records.[17] Specific claims databases included in this study were the MarketScan Inpatient Admissions and Outpatient Services databases, with 23.2 million inpatient admission summary records and 8.7 billion individual outpatient claim records, respectively, for individuals covered by commercial insurance providers. These databases assign patients a unique identification number, enabling longitudinal analysis and linkage between data sets. The Stanford Institutional Review Board considered use of these databases to be exempt from institutional review board review.

Variables

Using the Inpatient Admissions database, women who underwent abdominal free tissue transfer for breast reconstruction were identified based on CPT code. (**See Appendix, Supplemental Digital Content 1**, which provides the reader with a list of the exact International Classification of Diseases, Ninth Revision, and CPT codes that were used in the analysis, ***http://links.lww.com/PRS/E139***.) Accordingly, we were unable to distinguish between transverse rectus abdominis myocutaneous (TRAM) and muscle-sparing TRAM flaps, because of a shared CPT code for both procedures. Using the Outpatient Services database, women with a diagnosis of venous thromboembolism (deep venous thrombosis and/or pulmonary embolism) were identified by *International Classification of Diseases, Ninth Revision,* code. These two data sets were then merged by the unique patient identifier. The outcome variable, venous thromboembolism event, was defined as documented deep venous thrombosis and/or pulmonary embolism within 90 days of free abdominal tissue transfer for breast reconstruction. In instances of multiple encounters designating a diagnosis of

venous thromboembolism, the first encounter was considered the date of venous thromboembolism development. The study period was from 2007 to 2015, when *International Classification of Diseases, Ninth Revision,* codes were phased out.

Predictor (i.e., explanatory) variables extracted from the databases included age at reconstruction, date of reconstruction, timing of reconstruction in relation to mastectomy (immediate versus delayed), body mass index, history of radiation therapy, type of abdominally based free flap, history of venous thromboembolism, postoperative hematoma, and discharge status. The Elixhauser Comorbidity Index, a validated score based on weighted *International Classification of Diseases, Ninth Revision,* diagnosis codes and known association with comorbidity and mortality, was calculated to represent the degree of chronic medical comorbid disease.[18] Intraoperative data, including operative time, was not included, because this information is not available in the database. In addition, Truven MarketScan databases do not contain Caprini scores or the totality of variables required to create a Caprini score. For example, the Caprini score includes mobility status and laboratory data (e.g., homocysteine, lupus anticoagulant, and anticardiolipin antibody), which are not documented in the database.

Statistical Analysis

Fisher's exact and *t* tests were used for univariate analyses of patients who developed a venous thromboembolism during versus after hospital discharge. Given that venous thromboembolism was a binary outcome, multivariable logistic regression modeled predictors of venous thromboembolism. A nonparsimonious approach was chosen in light of historical variables associated with venous thromboembolism. To assess the effects of time with venous thromboembolism, Poisson regression was used considering adjusted venous thromboembolism events per year (i.e., a count outcome). Similar to the logistic model, the zero-inflated Poisson regression included a nonparsimonious inclusion of all baseline variables. Logistic model fitness was assessed using the C statistic. Values of $p < 0.05$ were considered significant. All analyses were conducted using Stata/SE Version 14.2 (StataCorp LLC, College Station, Texas).

RESULTS

A total of 12,778 women underwent free abdominal tissue transfer for breast reconstruction during the study period. Mean age at the time of reconstruction was 49.7 ± 8.0 years. Fifty-seven percent of reconstructions were TRAM flaps, 8881 cases (41.1 percent) were deep inferior epigastric perforator (DIEP) flaps ($n = 6402$), and a small minority of cases (1.2 percent) were superior inferior epigastric artery (SIEA) flaps ($n = 289$). Also, 868 patients (6.8 percent) had a body mass index greater than 25 kg/m^2, and 4193 patients (32.8 percent) underwent immediate reconstruction. Average Elixhauser Comorbidity Index was 1.36 ± 1.06, and medical history was notable for prior venous thromboembolism and radiation therapy in 90 (0.7 percent) and 1027 patients (8.12 percent), respectively. Mean length of stay was 4.31 ± 1.98 days.

Of these patients, 167 (1.3 percent) were diagnosed with a venous thromboembolism within 90 days of breast reconstruction. Eighty-two patients (49.1 percent) had a deep venous thrombosis only, 79 (47.3 percent) had a pulmonary embolism only, and six (3.6 percent) had both diagnoses. The distribution of venous thromboembolism events over time within the first 90 days is illustrated in Figure 1 and Table 1. Significant predictors of venous thromboembolism included an Elixhauser Comorbidity Index of 3 and greater than or equal to 4 (OR, 2.20; $p = 0.001$; and OR, 3.78; $p < 0.001$, respectively), history of venous thromboembolism (OR, 3.19; $p = 0.026$), and longer inpatient length of stay (OR, 1.11; $p < 0.001$), with a C statistic of 0.68 (Table 2). For each additional day admitted, the risk of a venous thromboembolism event increases by 0.5 percent (Fig. 2).

The majority of venous thromboembolism events [$n = 112$ (67.1 percent)] occurred after hospital discharge. Compared to patients who developed a venous thromboembolism during the index admission for breast reconstruction, patients who developed a venous thromboembolism after discharge had a lower mean Elixhauser Comorbidity Index (1.48 ± 0.10 versus 2.38 ± 0.19; $p < 0.001$) (Table 3). There were no significant differences in any other patient or clinical characteristics evaluated.

There was no significant difference in the rate of venous thromboembolism over time on zero-inflated Poisson regression, or based on direct comparison of early (2007 to 2009) and late (2013 to 2015) years (Table 4). Length of stay was significantly longer during the early period compared to the later period (4.36 days versus 4.13 days; $p < 0.001$).

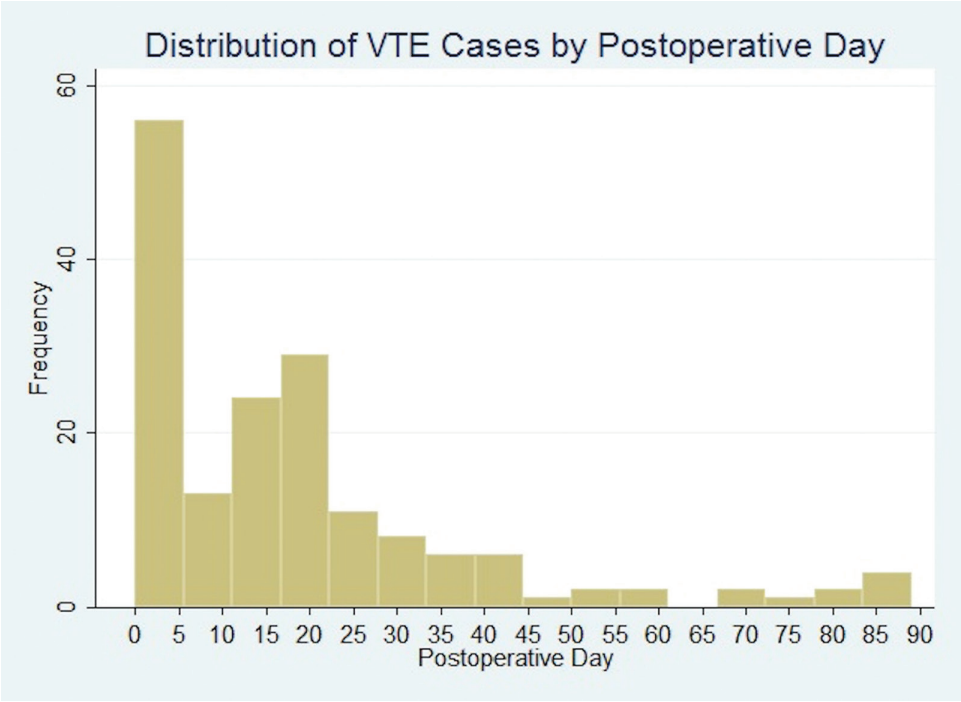

Fig. 1. Distribution of venous thromboembolism (*VTE*) cases by postoperative day. Distribution is illustrated over the 90-day postoperative period. The majority of venous thromboembolisms occurred after hospital discharge.

Table 1. Time to Venous Thromboembolism

Postoperative Days	Frequency* (%)
1–4	55 (32.9)
5–9	9 (5.4)
10–14	21 (12.6)
15–19	23 (13.8)
20–24	20 (12.0)
25–29	6 (3.6)
30–34	8 (4.8)
35–39	5 (3.0)
40–44	6 (3.6)
45–49	1 (0.6)
50–54	2 (1.2)
55–59	2 (1.2)
60–64	0 (0)
65–69	1 (0.6)
70–74	1 (0.6)
75–79	2 (1.2)
80–84	1 (0.6)
85–89	4 (2.4)

*Total $n = 167$.

DISCUSSION

Based on our nationwide analysis of 12,778 women who underwent free abdominally based breast reconstruction over a period of 8 years, the incidence of postoperative venous thromboembolism within 90 days of reconstruction is 1.3 percent. Significant predictors of venous thromboembolism include Elixhauser Comorbidity Index of 3 or greater than or equal to 4 ($p \leq 0.001$), history of venous thromboembolism ($p < 0.03$), and longer length of stay ($p < 0.001$). The correlation of higher Elixhauser Comorbidity Index with venous thromboembolism is not surprising, given previous work demonstrating an association between renal and pulmonary comorbidities, in addition to impaired patient functional status, with venous thromboembolism in this patient population.[19,20] Length of stay has also been previously shown to correlate with risk of venous thromboembolism,[6] although the directionality of this effect cannot be determined in our study. Unlike prior studies that have shown an association between age,[20,21] higher body mass index,[12,19,20] immediate reconstruction,[19,20] and history of radiation therapy[19] with venous thromboembolism, our study does not suggest that these are significant risk factors. Furthermore, longer surgical duration has also been cited as a significant risk factor for venous thromboembolism,[12,22] although this variable could not be evaluated in our study.

Our analysis also demonstrates that there is no significant difference in the rate of venous thromboembolism over time, or specifically between early (2007 to 2009) and late (2013 to 2015) periods, despite the shorter mean length of stay in the latter period ($p < 0.001$). Enhanced recovery after surgery pathways were first introduced in cardiac

Table 2. Multivariable Predictors of Venous Thromboembolism after Breast Reconstruction

Characteristic	VTE (%)	No VTE (%)	OR	95% CI	*p*
No.	167	12,611			
Mean age ± SD, yr	49.93 ± 7.84	49.70 ± 8.00	1.00	0.98–1.02	0.758
Immediate reconstruction	55 (32.9)	4138 (32.8)	0.94	0.67–1.30	0.696
BMI >25 kg/m^2	11 (6.6)	857 (6.8)	0.59	0.31–1.13	0.112
History of radiation therapy	10 (6.0)	1027 (8.2)	0.76	0.40–1.46	0.413
TRAM flap	114 (68.3)	8767 (69.5)	1.05	0.77–1.44	0.736
Elixhauser Comorbidity Index					
≤1	80 (47.9)	8028 (63.7)	Ref	—	—
2	41 (24.0)	2901 (23.0)	1.41	0.96–2.08	0.080
3	26 (15.6)	1167 (9.3)	2.20	1.38–3.50	0.001
≥4	20 (12.0)	515 (4.1)	3.78	2.22–6.42	0.000
History of VTE	4 (2.4)	86 (0.7)	3.19	1.15–8.90	0.026
Postoperative hematoma	18 (10.8)	625 (5.0)	1.63	0.97–2.74	0.064
Mean inpatient length of stay ± SD	5.77 ± 4.28	4.29 ± 1.94	1.11	1.07–1.15	0.000
Discharge to SNF	1 (0.6)	19 (0.2)	2.83	0.36–22.5	0.326

VTE, venous thromboembolism; BMI, body mass index; Ref, reference; SNF, skilled nursing facility.

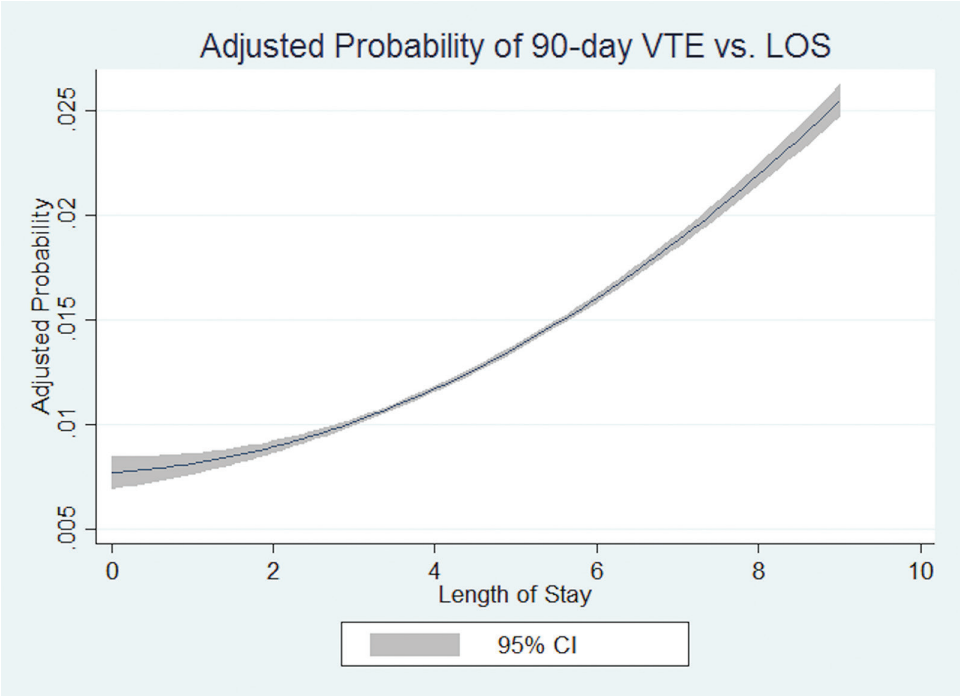

Fig. 2. Adjusted probability of 90-day venous thromboembolism (*VTE*) versus length of stay (*LOS*). For each additional day admitted, the risk of a thromboembolic event increases by 0.5 percent.

surgery in the 1990s,[23] were popularized in the context of colorectal surgery,[24–26] and have gained traction in the perioperative care of breast reconstruction patients within the past decade.[27] For abdominally based free autologous breast reconstruction, several authors have shown that institution of enhanced recovery after surgery pathways can reduce length of stay without increasing the rate of postoperative complications.[28–32] Based on current recommendations,[4] chemoprophylaxis is typically limited to inpatient stay, and patients with a shorter length of stay are presumably receiving fewer days of postoperative chemoprophylaxis. Our results not only illustrate this trend toward shorter length of stay in the latter period, but also suggest that the assumed concomitant fewer days of inpatient venous thromboembolism chemoprophylaxis is not associated with an increased risk of postoperative venous thromboembolism.

Regarding the timing of postoperative venous thromboembolisms, our study echoes emerging evidence that the risk of venous thromboembolism extends well into the postoperative period. We demonstrate that 32.9 percent of venous

Table 3. Comparison of Patients with Inpatient and Postdischarge Venous Thromboembolism Events

Characteristic	Inpatient VTE (%)	Postdischarge VTE (%)	*p*
No.	55	112	
Mean age ± SD, yr	50.43 ± 1.10	49.68 ± 0.73	0.559
Immediate reconstruction	14 (25.5)	41 (36.6)	0.165
BMI >25 kg/m^2	2 (3.6)	9 (8.0)	0.342
History of radiation therapy	3 (5.5)	7 (6.3)	1.000
Mean Elixhauser Comorbidity Index ± SD	2.38 ± 0.19	1.48 ± 0.10	0.000
History of VTE	3 (5.5)	7 (6.3)	1.000

VTE, venous thromboembolism; BMI, body mass index.

thromboembolisms occurred during the initial inpatient admission following breast reconstruction, whereas 67.1 percent occurred after discharge and within 90 days of reconstruction. This distribution is an exact match to the breakdown of inpatient and 90-day postdischarge venous thromboembolism events in Momeni and Fox's analysis of 52,547 women undergoing mastectomy with or without alloplastic or autologous reconstruction.[33] The study by Momeni and Fox and the study by Pannucci et al. examining venous thromboembolism events among plastic surgery patients within 60 days[7] suggest that the risk of postdischarge venous thromboembolism is particularly pronounced among higher risk patients. More generally, the Million Women Study showed that for middle-aged women in the United Kingdom undergoing surgery, the relative risk of venous thromboembolism peaks at 3 weeks postoperatively and remains elevated for up to 1 year after surgery.[34] In our comparison of patients who developed venous thromboembolisms as inpatients compared to after discharge, we found no significant difference between cohorts in terms of age, timing of reconstruction, body mass index, history of radiation therapy, or history of venous thromboembolism. Patients who developed a venous thromboembolism after discharge were more likely to have a lower Elixhauser Comorbidity Index ($p < 0.001$) compared to those who developed a venous thromboembolism as an inpatient. Collectively, these findings suggest that in contrast to findings of prior studies, it is the comparatively normal risk patients who are at increased risk of venous thromboembolism development after hospital discharge.

Table 4. Adjusted Rate of Venous Thromboembolism and Length of Stay by Period

Period	No. of Observations	Adjusted VTE Rate (%)	Mean LOS ± SD
2007–2009	3022	1.3	4.36 ± 2.13
2013–2015	4654	1.2	4.13 ± 1.69

VTE, venous thromboembolism; LOS, length of stay.

There are several theories to explain the continued postoperative occurrence of venous thromboembolisms, despite recommendations based on evidence of the protective effects of postoperative chemoprophylaxis. Explanations include lack of provider adherence to recommendations, and improper dosing of chemoprophylactic medications.[15] For instance, published clinical trials data have shown that accepted prophylactic regimens for postoperative anticoagulant dose may be inadequate for many patients; this is relevant because patients whose anticoagulant dose is inadequate are significantly more likely to develop a 90-day venous thromboembolism after plastic surgery requiring inpatient admission.[35] An additional hypothesis is that postoperative venous thromboembolisms are the consequence of rebound thrombin generation and depletion of tissue factor pathway inhibitor, both of which result in procoagulant effects secondary to discontinuation of unfractionated heparin or low-molecular-weight heparin.[36–38] However, the time course of these effects, specifically in relation to the distribution of venous thromboembolism cases by postoperative day, has yet to be determined.

Venous thromboembolism breakthrough events may also reflect insufficient duration of postoperative chemoprophylaxis. Several studies of patients undergoing orthopedic surgery[39,40] and abdominal or pelvic surgery[41–43] have illustrated the superiority of extended-duration chemoprophylaxis in preventing venous thromboembolism events in the postdischarge period, leading to recommendations for extended-duration chemoprophylaxis in at-risk cohorts. Perhaps the most well-known of these studies is the Enoxaparin and Cancer II study, which demonstrated that postoperative low-molecular-weight heparin prophylaxis for 4 weeks, compared to 1 week, following surgery for abdominal or pelvic cancers significantly reduced the rate of venous thromboembolism events at approximately 1 month postoperatively without an increased incidence of hematoma or other major adverse events.[41] In plastic surgery,

there has not yet been robust evidence to support extended-duration chemoprophylaxis, and thus there is no consensus recommendation on this topic.[4] In the absence of data, recent summary CME articles support that there is no standard of care for the duration of chemical prophylaxis beyond the inpatient stay.[44] Although our study demonstrates a high rate of postdischarge venous thromboembolisms and thus a potential role for extended-duration chemoprophylaxis, the lack of significant differences between patients who developed venous thromboembolisms as inpatients and after discharge suggests that stratifying risk by time among the venous thromboembolism cohort may be difficult. Patients who developed a venous thromboembolism after discharge were, on average, healthier with a lower mean Elixhauser Comorbidity Index compared to those who developed a venous thromboembolism as an inpatient, suggesting that patients on the lower end of the risk spectrum should not be ignored when determining eligibility for extended-duration chemoprophylaxis.

Limitations of our study are largely related to the nature of retrospective database analysis. Our analysis is confined to variables contained within our source database. We are therefore unable to reliably evaluate several elements related to patient characteristics (e.g., use of hormonal or other chemotherapy in the neoadjuvant setting, status of tissue expansion, laterality), operative characteristics (e.g., mixed delayed-immediate cases, concomitant operations, operative time), characteristics of the hospital course (e.g., use of compression stockings, inpatient chemoprophylaxis dosing and duration, patient mobility status, involvement of physical therapy), and diagnosis of venous thromboembolism (e.g., method of diagnosis). Although our national database lacks the granularity of single-institution studies and thus is restricted in the scope of analysis, our findings nonetheless demonstrate a national trend that can subsequently be studied on a more detailed level.

On a similar note, a significant advantage of this study in comparison to single-institution studies is the fact that the database should capture all venous thromboembolism events, including those diagnosed or managed at other sites. Future investigations could attempt to create a venous thromboembolism risk score based on administrative data that performs as well as the Caprini score, and should also evaluate the impact of hormonal therapy on venous thromboembolism development. Finally, additional investigation is needed to prospectively evaluate risk factors for inpatient and out-of-hospital venous thromboembolisms among autologous breast reconstruction patients to identify modifiable risk factors and patients to target for extended-duration chemoprophylaxis.

CONCLUSIONS

Postoperative venous thromboembolism among patients undergoing autologous free tissue transfer for breast reconstruction continues to be an inadequately addressed problem, as evidenced by a stable incidence over the study period. Although much attention has been directed to active venous thromboembolism prevention for inpatients using individualized venous thromboembolism risk stratification, pneumatic compression, and chemoprophylaxis, the majority of venous thromboembolism events in the 90-day postoperative period occur after discharge. An expanded focus should include discerning postoperative patients at risk for out-of-hospital venous thromboembolisms and identifying best practices to prevent postdischarge venous thromboembolisms.

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