Original Article

Evaluation of 30-Days Venous Thromboembolism (VTE) Following Autologous Breast Reconstruction

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ABSTRACT

Background: Venous thromboembolism (VTE) is one of the known medical complications in autologous breast reconstruction (ABR) which is associated with a short and long-term morbidity as well as mortality. Identifying VTE risk factors is crucial for appropriate VTE prophylaxis measurements to lower this complication following ABR.

Methods: Using American College of Surgeons National Surgery Quality Improvement Project database, we examined the clinical data of patients who underwent ABR from 2016-2020 in the US. The frequency of VTE, day of occurrences and risk factors associated with VTE were evaluated.

Results: Overall, 11,847 patients underwent ABR in the study period. The overall VTE rate was 1.0%. Totally 117 patients experienced VTE with a total occurrence of 127. Postoperative day 1 and 2 were reported with the highest frequency of VTE (21/127). Using multivariate regression analysis, independent risk factors associated with a higher VTE rate were length of hospital stay>=5 d [adjusted odd's ratio (AOR), 3.29], operative time longer than 10 h (AOR,2.17), and immediate reconstruction (AOR,1.51). Although free flap breast reconstruction was associate with a higher VTE rate compared with pedicled flap reconstruction (1.2% vs. 0.8%); however, multivariate regressing analysis did not show this factor as an independent VTE risk factor.

Conclusion: Being proactive to make the patients ready to discharge by POD-4 and having strategy to shorten the length of operation could help to lower the rate of VTE in ABR. Plastic surgeons should consider these factors and use appropriate prophylactic measures to minimize the risk of VTE development.

KEYWORDS
Risk factors; Venous thromboembolism; Autologous breast reconstruction

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INTRODUCTION

Autologous flap-based breast reconstruction is becoming a gold standard in patients who wish to achieve a more natural appearance and feel when compared to implant reconstruction[1,2]. Depending on the post-operative needs of these patients, the flexibility in patient selection for free flap reconstruction makes it a widely preferred procedure[3]. Using 2020 BREAST-Q scores, patient satisfaction with surgical outcome, sexual and psychosocial well-being is understood to be higher among autologous reconstruction than implant-based procedures[4-6]. These data provide crucial information pertaining to patient-centered care, suggesting the clinical importance of autologous flap-based approaches to breast reconstruction.

Venous thromboembolism (VTE) is a known postoperative complication in autologous breast reconstruction which this can be a serious complication, contributing significantly to post-procedural morbidity and mortality. VTE is constituted by two blood-clotting disorders: deep vein thrombosis (DVT) and pulmonary embolism (PE) [7]. As such, the high mortality rate constitutes PE as a problem deserving to identify risk factors associated with PE with the hope in modification of these risk factors to minimize this serious complication as well as adequate pre- and periprocedural prophylaxis. Aside from PE, DVT can lead to several additional consequences including post-thrombotic syndrome. The incidence of post-thrombotic syndrome in symptomatic DVT patients was found to be as high as 40%; 15% of whom experienced debilitating symptoms according to the Villalta scale[8]. Such postoperative complications suggest an importance for surgeons to understand and appropriately prevent VTE associated morbidity and mortality.

Due to subclinical DVT and PE presentation, the actual incidence of VTE may be higher than data suggests; therefore, plastic surgeons must be able to readily identify risk factors in autologous breast reconstruction cases. The Caprini risk assessment model (RAM) is the most extensively used metric in predicting an individual patient's risk for postoperative VTE [9]. The risk factors of the Caprini RAM most relevant to plastic surgery include age, Body Mass Index (BMI), medical history, hospital admission, immobility, type of surgery, length of stay, family history of VTE, and recent trauma or injury[9].

In this study we aimed to investigate the frequency and risk factors of VTE in patients who underwent autologous breast reconstruction with using a large database collected form the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) database to evaluate the rate of VTE within 30-days following autologous breast reconstruction and to identify independent risk factors of VTE in this patient population.

METHODS AND MATERIALS

Database: The American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database is a risk adjusted, surgical outcomes-based program designed to measure and improve the quality of surgical care. Trained clinical reviewers prospectively collect the ACS-NSQIP data and validated data from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity on all patients undergoing major surgeries at participant institutions. For example, in 2020, the ACS-NSQIP database contained 902,968 cases submitted from 706 NSQIP-participating sites. The ACS-NSQIP database provides prospective national data with a large sample size making it ideal for identifying important differences in patient risk [10].

Using the NSQIP database, we analyzed discharge data for female breast cancer patients with no age limitation who underwent autologous breast reconstruction surgery from 2016 to 2020. We used Current Procedural Terminology (CPT) codes of19361 (Breast reconstruction with latissimus dorsi flap), 19364 (Breast reconstruction with free flap), 19367 (Breast reconstruction with transverse rectus abdominis myocutaneous flap -TRAM-, single pedicle), 19368 (Breast reconstruction with TRAM flap, single pedicle with microvascular anastomosis), 19369 (Breast reconstruction with TRAM flap, double pedicle) to identify our patient population. The main outcome research was VTE within the 30 d postoperative period. The overall frequency and day of diagnosed VTE was tracked.

Perioperative factors that were analyzed included patient characteristics, patient comorbidities, smoking status, steroid use, BMI, free flap vs.

pedicled flap, length of operation and length of hospital stay (LOS). We were unable to evaluate the effect of chemotherapy and radiation as the majority of data were missing.

Statistical Analysis

Univariate and multivariate regression analysis were performed to identify independent predictors of VTE following autologous breast reconstruction. The adjusted odds ratio (AOR) was calculated in multivariate regression analysis to determine the combined effect of various perioperative factors (age, patient comorbidities, smoking, BMI, free flap vs. pedicled flap, length of operation and LOS) on VTE. All statistical analyses for the ACS-NSQIP were conducted using Statistical Package for the Social Sciences (SPSS) version 26 statistical software. Statistical significance was set at *P*-values<0.05 and odds ratio (OR) with the 95% confidence interval does not include the value of one. OR> 1 was considered the risk factor for VTE.

RESULTS

Overall, 11847 patients underwent autologous breast reconstruction in this database from 2016 to 2020. Examining patient characteristics, the mean age was 51.6 ± 10 yr old and 10.8% of patients were older than 65 yr old. The majority of reported race was Caucasian (60.3%), followed by African American (13.7%). The three most common comorbidities were hypertension (25.6%), diabetes mellitus (7.6%) and smoking (6.8%). The majority of the patients were classified in the American Society of Anesthesiologists physical status classification (ASA)-II (62.1%) and ASA-III (34.6%). Sixteen percent of patients had a BMI of 35 or higher (Table 1).

The most common type of autologous reconstruction was free flap-based reconstruction (free flap: 71% vs. pedicled flap: 29%). The majority of autologous breast reconstruction were delayed reconstruction (delayed: 63% vs. immediate: 37%). The mean operative time was 422 ±185 (min). The mean LOS

Table 1. The patient characteristics and comorbidity including overall frequency with and without VTE

	Without VTE	With VTE	Overall	P-value
Characteristics				
Age <65	99.1%	0.9%	89.2%	0.190
Age older than 65	98.7%	1.3%	10.8%	
Race				0.844
White	99.1%	0.9%	60.3%	
African-American	98.6%	1.4%	13.7%	
Asian	99.1%	0.9%	3.8%	
Not reported/low frequency race	99.1%	0.9%		
ASA Classification				0.347
I	99.1%	0.9%	2.8%	
II	99.0%	1.0%	62.1%	
III	99.0%	1.0%	34.6%	
IV	96.2%	3.8%	0.4%	
BMI				
<35	99.1%	0.9%	83.9%	**0.010**
>=35	98.5%	1.5%	16.1%	
Comorbidity				
Diabetes Mellitus	98.5%	1.5%	7.6%	0.144
Hypertension	98.9%	1.1%	25.6%	0.384
Smoker- current	99.0%	1.0%	6.8%	0.730
Sever COPD	96.9%	3.1%	0.5%	0.088
Sever Liver Disease	100%	0.0%	0.0%	0.888
CHF	99.9%	0.1%	0.1%	0.777
CKD n Dialysis	83.3%	16.7%	0.1%	**0.000**
Metastatic cancer	99.5%	0.5%	1.6%	0.519
Chronic Steroid use	99.5%	0.5%	1.6%	0.531
Weight loss>10%	100%	0.0%	0.2%	0.655
Bleeding disorders	98.7%	1.3%	0.7%	0.783

was 3.4 ± 3.7 (days) (Table 2).

The overall VTE rate was 1.0%. Overall, 117 patients experienced VTE with a total occurrence of 127. VTE has been reported from postoperative day (POD)-1 to POD-29 (mode: POD-2; median: POD-14). POD-1 and POD-2 were reported with the highest frequency of VTE (21/127) (Figure 1).

Univariate (Table 3) and multivariate (Table 4) regression analyses were performed to identify risk factor associated with a higher VTE rate in this patient population. Using multivariate regression analysis, independent risk factors associated with a higher VTE rate were 1) LOS >=5 d (adjusted odd's ratio [AOR], 3.29; confidence interval [CI]: 2.24 - 4.32; *P*<0.001), 2) operative time longer than 10 hours (AOR, 2.17; CI: 1.45 - 3.24; *P*<0.001) and 3) immediate reconstruction (AOR, 1.51; CI: 1.05 - 2.19; *P*<0.001). Although, univariate regression analysis showed BMI>35 and free flap breast reconstruction were associated with a higher VTE

Table 2. Operative characteristics including overall frequency with and without VTE

	Without VTE	With VTE	Overall	P-Value
Autologous Breast Reconstruction Types				
Latissimus dorsi flap	99.8%	0.2%	2,532 (21.4%)	**<0.001**
Free flap	98.8%	1.2%	8,297 (70.1%)	
TRAM*- Unilateral pedicled	98.3%	1.7%	858 (7.3%)	
TRAM-Bilateral pedicled	100%	0.0%	142 (1.2%)	
Free vs. pedicled flap				
Free flap	98.8%	1.2%	8,398 (71%)	**0.001**
Pedicled flap	99.5%	0.5%	3,431 (29%)	
Immediate vs. delayed				
Immediate	98.7%	1.3%	4,406 (37.2%)	**0.003**
Delayed	99.2%	0.8%	7,423 (62.8%)	
Operative Time				
< 6 hours	99.4%	0.6%	4,550 (38.5%)	**<0.001**
6-8 hours	99.2%	0.8%	3,021 (25.5%)	
8-10 hours	99.2%	0.8%	2,342 (19.8%)	
>10hours	97.6%	2.4%	1,916 (16.2%)	
Length of Hospital Stay (Days)				**<0.001**
=< 3	99.5%	0.5%	6,558 (55.4%)	
4	99.1%	0.9%	3,065 (25.9%)	
5	98.0%	2.0%	1,183 (10.0%)	
>= 6	96.7%	3.3%	1,023 (8.6%)	

*TRAM: Transverse Rectus Abdominus Muscle Flap

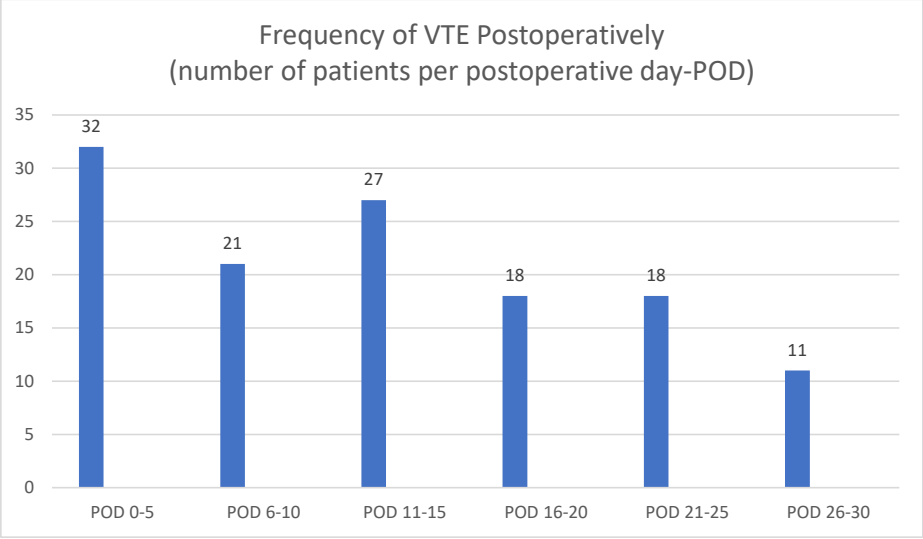

Figure 1. Frequency of VTE within 30-day postoperatively in autologous breast reconstruction

Table 3. Univariate regression analyses associated with VTE in patients who underwent Autologous Breast Reconstruction

	Odds Ratio	95% Confidence Interval	P-value
Characteristics			
Age			
<65	Reference	Reference	Reference
older than 65	1.41	0.84 – 2.37	0.19
BMI			
<35			
>=35	1.73	1.13 – 2.64	0.01
Comorbidity			
Diabetes Mellitus	1.54	0.86 – 2.75	0.147
Hypertension	1.95	0.80 – 1.78	0.384
Smoker- current	0.87	0.41 – 1.88	0.731
Sever COPD	3.22	0.78 – 13.30	0.11
Sever Liver Disease	NS	NS	NS
Congestive Heart Failure	NS	NS	NS
Chronic Kidney Disease in Dialysis	20.18	2.34 – 174.12	**0.006**
Metastatic cancer	0.53	0.07 – 3.80	0.53
Weight loss>10%	NS	NS	NS
Bleeding disorder	1.32	0.18 – 9.57	0.78
Free vs. pedicled flap			
Free flap	2.42	1.44 – 4.05	0.001
Pedicled flap	Reference	Reference	Reference
Immediate vs. delayed			
Immediate	1.73	1.20 – 2.48	0.003
Delayed	Reference	Reference	Reference
Operative Time			
< 10 hours	Reference	Reference	Reference
>10 hours	3.41	2.34 – 4.96	<0.001
Length of Hospital Stay (Days)			
< 5	Reference	Reference	Reference
>= 5	4.38	3.04 – 6.31	<0.001

rate; however, these factors were not found to be an independent risk factor in multivariate regression analysis. Moreover, age, diabetes mellitus and smoking were not associated with a higher VTE rate.

DISCUSSION

VTE is a significant cause of postoperative morbidity and mortality in breast reconstruction cases of which autologous flap-based approaches are becoming regarded as the gold-standard for breast reconstruction. For this reason, it's important to investigate the current and historical rate of VTE occurrence in this population to determine the relevant risk factors. Our findings produced a VTE rate of 1.0% within 30 d following surgery. Other studies have reported a range of overall VTE rates in similar patient populations from 0.13% - 6.8%[11-13]. Moreover, our study showed that the majority of VTE occurred after discharge with the highest frequency of cases reported during POD-1 and POD-2 (16.5%). Similarly, Rochlin et al.[13] in a large nationwide study in women who underwent free abdominally based breast reconstruction showed VTE rate of 1.3% within 90 d of reconstruction. Similarly, they showed the majority of VTE (67.1%) occurred following discharge.

To better contextualize these findings, our data specifies risk factors for VTE occurrence were LOS ≥ 5 d (AOR, 3.29), the length of the operation ≥ 10 h (AOR: 2.17) and immediate breast reconstruction (AOR: 1.51). Previous studies have identified a similar correlation between LOS and risk for thromboembolism, reporting post-operative days 1-4 with the highest frequency of VTE[13-15]. Rochlin et al.[13] showed the risk of VTE increases by 0.5% for each additional hospital stay. In addition, Fischer et al.[16] in a study evaluating VTE risk factors in patients undergoing mastectomy and immediate reconstruction showed when controlling

Table 4. Multivariate regression analysis associated with VTE in patients who underwent Autologous Breast Reconstruction

Risk Factors	Adjusted Odds Ratio	95% Confidence Interval	P-value
Patient Characteristics			
Age			
=<65	Reference	Reference	Reference
>65	1.59	0.93 - 2.74	0.09
BMI			
<35	Reference	Reference	Reference
>=35	1.45	0.94 – 2.24	0.09
Comorbidity			
Hypertension	1.02	0.66 – 1.57	0.93
Diabetes Mellitus	1.37	0.74 – 2.55	0.31
Smoker- current	0.90	0.41 – 1.94	0.78
Chronic Steroid use	0.54	0.08 – 3.93	0.54
Bleeding Disorders	1.22	0.16 – 8.96	0.85
Free vs. pedicled flap			
Free flap	1.59	0.93 – 2.73	0.09
Pedicled flap	Reference	Reference	Reference
Immediate vs. delayed			
Immediate	1.51	1.05-2.19	0.03
Delayed	Reference	Reference	Reference
Operative Time			
=< 10 hours	Reference	Reference	Reference
>10 hours	2.17	1.45 – 3.24	<0.001
Length of Hospital Stay (Days)			
< 5	Reference	Reference	Reference
>= 5	3.29	2.24 – 4.82	<0.001

*NS: Non significant

for procedure type, operative time remained a significant VTE risk factor in which each additional hour operative time conferred 13% greater odds of VTE risk.

After a surgical procedure, rates of thrombosis can be exacerbated by non-ambulatory hospitalization. The connection between development of VTE and lengths of operation and/or hospital stay is likely due to an imbalance in the patient's coagulable state. Therefore, having an appropriate surgical strategy which could entail preop imaging locating perforators, having a dedicated OR team including anesthesiology and OR staff who are familiar with these surgical procedures as well as having a co-surgeon would be important factors to shorten the operation time. Escandon et al.[17] in a systematic review and meta-analysis study evaluating the value of a co-surgeon in microvascular breast reconstruction showed that a co-surgeon optimized efficacy and reduced the surgical time and length of stay.

Batdorf et al.[18] showed a significant shorter mean LOS with Enhanced recovery after surgery (ERAS) pathways than traditional care in patient who underwent free flap breast reconstruction (3.9 vs 5.5 d; P<0.001). ERAS pathways have been shown in multiple surgical specialties to decrease LOS after surgery, as well as in patients undergoing microvascular breast reconstruction[19]. The ERAS protocol is a multimodal, and evidence-based approach to perioperative management including preoperative and intraoperative measures to prevent hypothermia, reduction of opioid use after surgery (e.g. use of the combination of acetaminophen and NSAIDs with or without opioids), resume oral intake as soon as possible preferably within 24 hours after surgery and early mobilization are main goals. The goal of ERAS programs is to promote rapid recovery as quantified by decreasing the length of hospital stay, complications, and cost of specific surgical interventions[19].

Moreover, our study found immediate breast reconstruction as an independent risk factor for developing postoperative VTE (AOR: 1.51). Similarly, Fischer et al.[16] using multivariate regression analysis showed immediate breast construction as an independent risk factor for VTE in patient who undergoing mastectomy with

reconstruction (autologous [OR: 2.14] or implant based [OR: 1.65]) compared with patients who did not have reconstruction. This is likely related to the presence of neoplasm well established strong risk factor for VTE, thereby placing breast cancer patients and those undergoing reconstruction at a significant risk for VTE[20,21].

The current study showed that patients with BMI>35 had a significantly higher VTE rate compared with patients with lower BMI (1.5% vs. 0.9%; *P*= 0.01). Moreover, univariate regression analysis showed BMI > 35 was associated with a higher VTE rate (OR, 1.73; CI: 1.13-2.64; *P*=0.01) (Table 3); however, this factor was not found to be an independent risk factor in multivariate regression analysis after adjusting other factors. This is inconsistent with some previous studies which establish obesity as an independent risk factor for VTE [11,22]. Explanatory hypotheses for this association range from positing obesity as a proxy for a sedentary lifestyle to inflammation-mediated VTE caused by an increase in C-reactive peptide. The latter is supported by the physiological process by which adipose tissue releases inflammatory substances, leading to insulin resistance and endothelial dysfunction. By consequence, the coagulation cascade can be activated and promote the occurrence of thromboembolic events [23].

Interestingly, diabetes mellitus (DM), age>65 yr, and smoking were not associated with an increased risk of VTE. Additionally, while univariate analysis showed an association between chronic kidney disease and increased risk for VTE, multivariate analysis did not. Previous findings similarly suggest that DM and smoking are not associated as an independent VTE risk factor[11]. However, there are studies have found old age to be associated with an increased risk of VTE[11, 24].

There are limitations to this retrospective study similar to studies using a large database. The ACS-NSQIP collects the complications up to 30 d postoperatively; therefore, any complications after 30-day would not be captured. However; Rochlin et al.[13] who studied the frequency of VTE up to 90 d in free flap breast reconstruction showed only 20% postop VTE occurred after 30 d. Moreover, we were unable to evaluate the effect of chemotherapy and radiation therapy on VTE in these patients. However, Masoomi, et at.[11] using the Nationwide In-patient Sample (NIS) database showed prior chemotherapy was a significant risk factor for postoperative VTE (AOR, 3.5) in patients undergoing autologous breast reconstruction.

While studies have found strong associations between chemotherapy treatment for breast cancer and VTE development, it would be valuable to see how an additional variable, such as autologous breast reconstruction, may influence those findings[25]. Also, Fischer et al.[16] using the ACS-NSQIP database found radiation therapy within 90 d from surgery as risk factor of VTE. They have contributed this finding to the more advanced or aggressive cancer in these patients which likely increased the odds of VTE.

Additionally, we were unable to determine application of chemoprophylaxis (e.g., what type, dosage, length of use) which as in important factor in occurrence of VTE. Based on The American Society of Plastic Surgeons- VTE task force in 2023; there is no high-quality studies are available on the ideal duration of chemoprophylaxis in plastic surgery patients[26]. However, Consensus Review of Optimal Perioperative Care in Breast Reconstruction by ERAS Society recommended unless contraindicated, and balanced by the risk of bleeding, patients at a higher risk should receive low-molecular-weight heparin or unfractionated heparin until they are ambulatory or discharged[27]. Despite the limitations, the findings from our study suggest a more accurate timeframe on how specific lengths of hospital stay and surgical duration can elevate risk for VTE occurrence following autologous flap-based breast reconstruction. Specifically, the highest rate of VTE was found to have occurred within two days of the operation.

CONCLUSION

The overall VTE occurrence in autologous breast reconstruction was 1% within 30 d from surgery using a large nationwide database. This frequency alongside the findings pertaining to LOS>5 d and surgery length>10 h indicate a need for plastic surgeons to have appropriate strategies to shorten length of operation and post-operative hospitalization which could entails 1) preop planning including imaging study to locate perforators 2) being efficient in the operating room with having a dedicated operating team as well as having co-surgeon and 3) considering ERAS protocol postoperatively to shorten the length of

hospital stay. Future research can be aimed to better elucidate the optimal approach to DVT prophylaxis regimen and duration.

ETHICAL APPROVAL

This study was presented as a poster at the American Society for Reconstructive Microsurgery Annual Meeting, January 20-24, 2023 at the JW Marriott Turnberry in Aventura, Florida.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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