Pulmonary Embolism after Abdominal Flap Breast Reconstruction: Prediction and Prevention

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Background: Symptomatic pulmonary embolism constitutes a significant risk following abdominal flap breast reconstruction. Reported rates vary from 0 to 6 percent. The authors assessed risk factors associated with symptomatic pulmonary embolism and constructed a prediction model to identify high-risk patients.

Methods: Patients undergoing deep inferior epigastric perforator or transverse rectus abdominis musculocutaneous flap breast reconstructions at two academic centers from January of 2005 through January of 2011 were included. Thromboprophylaxis measures included early ambulation, low-molecular-weight heparin, elastic stockings, A-V Impulse System foot pumps, and pneumatic stockings. Risk factors for symptomatic pulmonary embolism were analyzed and weights were assigned to these risk factors. Sensitivity and specificity were maximized using receiver operating characteristic curves.

Results: Of 430 consecutive patients, symptomatic pulmonary embolism occurred in 17 cases (4.0 percent). Two independent predictors for symptomatic pulmonary embolism were found, body mass index higher than 25, additionally higher than 28, and the *BRCA* gene mutation. Operation duration and bilaterality of reconstructions were dependent on the *BRCA* mutation and both indirect predictors for symptomatic pulmonary embolism. Optimization of sensitivity and specificity resulted in a prediction model. No significant differences in efficacy were found between the different thromboprophylaxis measures.

Conclusions: The rate of symptomatic pulmonary embolism was 4.0 percent, despite standard thromboprophylaxis. Body mass index and *BRCA* were significant predictors for symptomatic pulmonary embolism. The authors integrated these factors into a prediction model, which provides a useful tool for identification of high-risk patients. This latter category may benefit from a more aggressive thromboprophylaxis approach. (*Plast. Reconstr. Surg.* 131: 1213, 2013.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Despite thromboprophylaxis measures, symptomatic pulmonary embolism remains a significant risk and a potentially lethal complication after abdominal flap breast reconstruction.[1–12] Rates of symptomatic pulmonary embolism after abdominal flap breast reconstruction vary from 0 to 6.3 percent.[1–11] Thromboembolic complications such as deep venous thrombosis and pulmonary embolism often have a subclinical course. Consequently, incidence rates reported in the literature are likely to be an underestimation. Indeed, the combined incidence of symptomatic and asymptomatic pulmonary embolism after immediate transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction was found to be 20.4 percent.[13]

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Abdominal flap breast reconstruction involves several important risk factors for venous thromboembolism.[11] Total anesthesia time often exceeds 6 hours, especially when reconstruction is directly preceded by mastectomy (primary reconstruction). Furthermore, in primary cases after therapeutic mastectomy the presence of malignancy adds to the thrombogenic nature of the intervention.[14] Also, an average age older than 45 years in this patient population constitutes a concomitant risk factor for venous thromboembolism.[14] The presence of sufficient abdominal fat is a prerequisite for abdominal flap breast reconstruction. Overweight, however, is a known risk factor for pulmonary embolism.[10] Finally, cancer-specific therapies such as chemotherapy, hormonal therapy, and radiotherapy constitute additional factors that may induce venous thromboembolism.[15]

In predicting the risk of venous thromboembolism, the Caprini Risk-Assessment Model has been applied. This model has been validated as a predictor of venous thromboembolism in different surgical specialties,[16–18] including plastic surgery.[19] The modified version of the Caprini Risk-Assessment Model, known as the Davison-Caprini Risk-Assessment Model, pertains to general plastic surgery.[19] Given the wide variability in patient-specific venous thromboembolism risk factors, the generic nature of this risk-assessment model can make it inaccurate for the individual patient undergoing abdominal flap breast reconstruction.

It is imperative that the risk of symptomatic pulmonary embolism and asymptomatic pulmonary embolism after abdominal flap breast reconstruction be fully recognized and that it is acknowledged that the incidence of asymptomatic pulmonary embolism is likely to be much higher. Development of an accurate predictive model, with increased predictive power for symptomatic pulmonary embolism in the setting of abdominal flap breast reconstruction, may be a valuable adjunct to clinical experience. Based on this risk-assessment model, patients could be assigned to an appropriate venous thromboembolism risk category before abdominal flap breast reconstruction.

Therefore, we evaluated the outcomes of 6 years of experience at two academic centers, both homogenous in their population and perioperative procedures. The objective was to accurately evaluate the incidence of symptomatic pulmonary embolism in patients undergoing abdominal flap breast reconstruction and to specify the relative contribution of established risk factors for symptomatic pulmonary embolism. In addition, we developed a risk-assessment model specifically for abdominal flap breast reconstruction to better define patients at increased risk of symptomatic pulmonary embolism and to formulate cutoff points for specific risk factors which, if exceeded, would mean a substantial increase in the risk of symptomatic pulmonary embolism.

PATIENTS AND METHODS

All consecutive patients who underwent deep inferior epigastric perforator (DIEP) or TRAM flap breast reconstruction at the Erasmus MC, University Medical Center Rotterdam and Maastricht University Medical Centre between January of 2005 and January of 2011 were included in this retrospective review. Patient demographics and perioperative data were collected. The primary outcome was the incidence of symptomatic pulmonary embolism. Other types of venous thromboembolism were excluded from analysis. Any episode of symptomatic pulmonary embolism occurring within 30 days after surgery was documented and included in the analysis.

At both centers, the postoperative thromboprophylaxis regimens consisted of perioperative elastic compression devices, early ambulation, and low-molecular-weight heparin [Nadroparine 5700 aXa-IE (= 0.6 ml, Fraxiparine; GlaxoSmithKline, Brentford, United Kingdom)]. Low-molecular-weight heparin was administrated subcutaneously 12 hours before surgery and continued once daily 12 hours postoperatively. Patients received rocuronium bromide (0.15 to 0.50 mg/kg) as a muscle relaxant during induction of general anesthesia and during dissection of the perforators within the rectus abdominis muscles. Elastic compression devices were applied preoperatively and were continued until full mobilization. In the early postoperative period, patients were positioned and nursed in a low- or semi-Fowler position. Mobilization was initiated on the first postoperative day, starting with bedside mobilization that was increased to walking in the days following.

Patients presenting with symptoms of pulmonary embolism (i.e., chest pain, shortness of breath, tachypnea, tachycardia, and decreased oxygen saturation) were screened for pulmonary embolism using the Wells criteria. Patients who scored more than 4 points underwent computed tomographic angiography. In accordance with Dutch guidelines, all patients with proven pulmonary embolism were treated with coumarins for a period of 6 months.

Patient-specific risk factors that were analyzed as potential predictors for symptomatic pulmonary

embolism after abdominal flap breast reconstruction included age, body mass index, *BRCA1* and *BRCA2* gene mutations, smoking, a history of cancer, presence of malignancy at the time of reconstruction, chemotherapy or hormonal therapy at the time of reconstruction, or previous radiotherapy. Perioperative variables that were analyzed as potential predictors included timing of reconstruction (primary or secondary), laterality of reconstruction (unilateral or bilateral), operation duration, the use of different elastic compression devices [i.e., A-V Impulse System (Covidien, Mansfield, Mass.) foot pumps, pneumatic stockings, elastic stockings], the number of reoperations, and the occurrence of complications other than pulmonary embolism.

Statistical Analysis

The effects of potential predictors for pulmonary embolism were analyzed using Fisher's exact tests for dichotomous variables, chi-square tests for categorical variables, and Mann-Whitney *U* tests for continuous variables. We performed a backward logistic regression analysis with symptomatic pulmonary embolism as the dependent variable and relevant variables (body mass index, smoking, oncologic mastectomy, *BRCA* gene, radiotherapy, primary/secondary reconstruction, operation time, number of reoperations, previous thromboembolic events, and mechanical thromboprophylaxis) as initial independent variables.

For easy use of the screening instrument, significant continuous covariates were categorized into two, three, or four equal sized categories. Separate models were postulated including these categorized covariates. Receiver operating characteristic curve analyses were performed, and the best model was selected on the basis of the largest area under the curve. Version 20.0 of IBM-SPSS (IBM Corp., Armonk, N.Y.) was used for statistical analyses. Two-sided values of $p < 0.05$ were considered statistically significant.

RESULTS

In our series, 430 consecutive patients underwent 592 breast reconstructions. A total of 261 patients were included from Erasmus MC, University Medical Center Rotterdam, and 169 patients were included from Maastricht University Medical Centre. Patient demographics were similar in both centers (Table 1). At both medical centers DIEP flaps were favored over TRAM flaps. Timing of reconstruction was mostly secondary. At Erasmus MC, University Medical Center Rotterdam, DIEP flaps were used more frequently ($p = 0.03$), whereas primary reconstructions were more frequently performed at Maastricht University Medical Centre ($p < 0.001$). Also, hospitalization was significantly longer at Erasmus MC, University Medical Center Rotterdam compared with Maastricht University Medical Centre ($p = 0.01$). Overall complication rates including the occurrence of symptomatic pulmonary embolism did not differ significantly between the two centers (Maastricht University Medical Centre, 33 percent; Erasmus MC, University Medical Center Rotterdam, 28 percent; $p = 0.33$).

Symptomatic pulmonary embolism occurred in 17 cases, resulting in an overall incidence rate of 4.0 percent (Maastricht University Medical Centre, 2.4 percent; Erasmus MC, University Medical Center Rotterdam, 5.0 percent; $p = 0.21$). The incidences of general complications and flap-related complications were similar in the symptomatic pulmonary embolism group and the non–symptomatic pulmonary embolism group (Table 2). No mortalities occurred and all patients recovered well from their episode of symptomatic pulmonary embolism. In accordance with Dutch guidelines for treatment of primary venous thromboembolism, we did not perform standard preoperative or postoperative laboratory assessments for coagulation abnormalities in these patients, because none of them had a positive family history or had experienced a previous episode of venous thromboembolism.

Symptomatic pulmonary embolism occurred in the early postoperative period, with a range of 2 to 10 days. One patient developed multiple pulmonary embolisms 2 days after discharge, for which she was readmitted. One patient took off her A-V Impulse System foot pumps systematically because she felt uncomfortable wearing them. In another patient, atrial fibrillation was thought to be the cause of symptomatic pulmonary embolism, as this occurred de novo postoperatively without any signs of deep venous thrombosis.

No significant differences in efficacy were found between the different elastic compression devices used. The reconstructive technique (DIEP or TRAM flap) did not influence the risk of symptomatic pulmonary embolism either ($p = 0.61$) (Tables 3 and 4).

Body mass index and *BRCA* gene mutations were significantly related to symptomatic pulmonary embolism (body mass index, $p = 0.001$; *BRCA*, $p = 0.01$) (Tables 3 and 4). A nonsignificant trend was observed that operation duration ($p = 0.07$)

Table 1. Baseline Demographics and Surgical Intervention Characteristics in 430 Abdominal Flap Breast Reconstruction Patients

	EMC (%)	MUMC (%)	*p*
No.	261	169	
Patient characteristics			
Age, yr			0.54*
Mean ± SD	47.5 ± 9.0	47.9 ± 8.6	
Range	27–73	23–70	
BMI, kg/m²			0.09*
Mean ± SD	27.2 ± 3.7	26.4 ± 4.0	
Range	19.2–37.7	19.5–39.0	
Perioperative characteristics			
Total operating time, hr			0.18*
Mean ± SD	7.8 ± 2.2	8.2 ± 2.6	
Range	3.5–14.20	3.2–16.0	
Total operating time for unilateral reconstruction, hr			0.02*
Mean ± SD	6.5 ± 1.3	7.0 ± 1.8	
Range	3.5–11.0	3.2–13.2	
Total operating time for bilateral reconstruction, hr			0.82*
Mean ± SD	10.0 ± 1.8	10.1 ± 2.6	
Range	5.0–14.2	4.3–16.0	
Hospitalization duration, days			0.01*
Mean ± SD	8.7 ± 5.5	7.6 ± 2.4	
Range	5–55	0–21	
Davison-Caprini total scores			0.57*
Mean ± SD	5.5 ± 1.4	5.6 ± 1.1	
Range	2–10	3–10	
Surgical characteristics			
Flap type			0.029†
DIEP	252 (96.6)	154 (91.1)	
TRAM	9 (3.4)	15 (8.9)	
Laterality of breast reconstruction			0.76†
Unilateral	161 (61.7)	107 (63.3)	
Bilateral	100 (38.3)	62 (36.7)	
Timing of breast reconstruction			<0.001†
Primary	48 (18.4)	72 (42.6)	
Secondary	191 (73.2)	87 (51.5)	
Combined reconstruction	22 (8.4)	10 (5.9)	
Potential risk factors for SPE			
Smoking	19 (7.3)	7 (4.1)	0.22†
Adjuvant therapy (chemotherapy, hormonal therapy, radiotherapy)	109 (41.8)	73 (43.27)	0.84†
Previous thromboembolic events	3 (1.1)	1 (0.6)	1.00†
BRCA1/BRCA2 gene mutation	60 (23.0)	29 (17.2)	0.18†

EMC, Erasmus MC, University Medical Center Rotterdam; MUMC, Maastricht University Medical Center; BMI, body mass index; SPE, symptomatic pulmonary embolism.
*Mann-Whitney *U* test.
†Fisher's exact test.

and bilateral reconstruction ($p = 0.08$) were related to symptomatic pulmonary embolism.

Positive *BRCA* status and bilateral reconstruction were both associated with a significantly longer operation duration compared with *BRCA*-negative status and unilateral reconstruction (*BRCA*-negative versus *BRCA*-positive: 7.4 versus 10.2 hours, $p < 0.001$; unilateral versus bilateral reconstruction: 6.7 versus 10.0 hours, $p < 0.001$). Prediction models including the univariately identified symptomatic pulmonary embolism predictors (body mass index, *BRCA* gene mutations, operation duration, and bilaterality) yielded areas under the curve in the range of 0.652 to 0.683.

In the backward logistic regression analysis, body mass index and *BRCA* status remained significant predictors (Table 5). In the prediction models, using a weight of 2 for positive *BRCA* status and a dichotomous body mass index resulted in an area under the curve of 0.718 and a body mass index in three equal sized categories in an area under the curve of 0.782. In addition, body mass index in four equal sized categories resulted in an area under the curve of 0.740. Using a weight of 1 for positive *BRCA* status and a dichotomous body mass index resulted in an area under the curve of 0.718 and a trichotomous body mass index in an area under the curve of 0.814, and body mass index in four categories resulted in an area under the curve of 0.753. It was concluded that the prediction model using *BRCA* with weight 1 and body mass index in three

Table 2. General and Flap-Related Complications in Patients with and without Symptomatic Pulmonary Embolism

Complication	Cases without SPE	Cases with SPE	*p**
No.	413	17	
General complications, %			
Pneumothorax	0.5	0.0	1.00
Seroma	1.2	0.0	1.00
Hematoma leading to reoperation	7.5	5.9	1.00
Infection	4.1	0.0	1.00
Wound healing problems	2.2	0.0	1.00
Flap-related complications, %			
Arterial thrombosis	1.5	5.9	0.25
Venous thrombosis	1.7	0.0	1.00
Venous congestion	3.1	5.9	0.44
Partial flap necrosis	7.0	0.0	0.62
Complete flap failure	3.9	0.0	1.00

SPE, symptomatic pulmonary embolism.
*Fisher's exact test.

categories (<25, 25 to 28, and >28), using a cutoff score of 2 or higher was the most efficient model. The body mass index cutoff values derived from this approach differed from the World Health Organization standards for overweight and obesity. Using the World Health Organization classification (<25, 25 to 30, and >30) resulted in an area under the curve of 0.744. The most efficient model is defined by Equation 1.

$$\text{Risk factor} = \textit{BRCA} + \text{body mass index} \geq 25 + \text{body mass index} \geq 28 \quad (1)$$

This model results in a score between 0 and 3. Thus, for example, a woman carrying the *BRCA* mutation, with a body mass index of 30, will have the risk score of 1 + 1 + 1 = 3, and is categorized as high risk. A woman not carrying the *BRCA* mutation with a body mass index of 26 will get the score 0 + 1 + 0 = 1 and is classified as low-risk.

Cutoff scores, sensitivity, specificity, overall accuracy, and areas under the curve of the most efficient model, the second best, and one using the World Health Organization cutoff scores are presented in Table 6. Receiver operating characteristic curves are depicted in Figure 1. The determination of cutoff scores is a tradeoff between sensitivity and specificity, and false-negatives and false-positives. Patients exceeding a specific cutoff score would be at higher risk for symptomatic pulmonary embolism after abdominal flap breast reconstruction.

DISCUSSION

Symptomatic pulmonary embolism is a potentially fatal complication after abdominal flap breast reconstruction and is associated with significant morbidity.[20–22] Reported incidence rates vary from 0 to 6 percent, in spite of standard thromboprophylaxis.[1–11] Among plastic surgical procedures, the risk of symptomatic pulmonary embolism is highest in liposuction, with a reported maximum incidence of 23 percent.[23] Breast reconstruction is second, with a maximum incidence of 6.0 percent, followed by thermal injuries (4.4 percent), abdominoplasty (0.3 to 3.4 percent), and oncologic head and neck reconstruction (0.1 to 0.4 percent).[16,23–25]

The current study focused on the incidence of symptomatic pulmonary embolism after abdominal flap breast reconstruction at two academic centers. In our series, 430 consecutive patients underwent 592 breast reconstructions. Symptomatic pulmonary embolism occurred in 17 cases, resulting in an incidence rate of 4.0 percent.

Risk Factors for Symptomatic Pulmonary Embolism

Significant predictors for symptomatic pulmonary embolism were body mass index and *BRCA* gene mutations. Statistically nonsignificant predictors were operation duration and bilateral reconstruction (Table 5). In the following paragraphs, each individual risk factor is discussed.

Table 3. Risk Factors for Symptomatic Pulmonary Embolism after Abdominal Flap Breast Reconstruction

Risk Factors for SPE	Cases without SPE	Cases with SPE	*p**
No.	413	17	
Age, yr	47.7 ± 8.9	46.9 ± 8.4	0.62
BMI, kg/m^2	26.7 ± 3.8	29.8 ± 2.4	<0.001
Operation duration, hr	7.9 ± 2.4	9.0 ± 2.4	0.07
Davison-Caprini total score	5.5 ± 1.3	5.5 ± 1.3	0.98
Hospitalization, days	8.0 ± 4.5	11.6 ± 3.2	<0.001
No. of reoperations	0.3 ± 0.5	0.2 ± 0.4	0.97

SPE, symptomatic pulmonary embolism; BMI, body mass index.
*Mann-Whitney *U* test.

Table 4. Risk Factors for Symptomatic Pulmonary Embolism after Abdominal Flap Breast Reconstruction

Risk Factors for SPE	Cases without SPE (%)	Cases with SPE (%)	*p**	Odds Ratio
No.	413	17		
BMI categories				
<25 kg/m²	158 (38.3%)	0 (0%)	0.001†	
25–28 kg/m²	130 (31.5%)	3 (17.6%)	0.23†	
28–30 kg/m²	41 (9.9%)	5 (29.4%)	0.01†	
>30 kg/m²	84 (20.3%)	9 (52.9%)	0.004†	
Smoking	25 (6.1%)	1 (5.9%)	1.00	0.97
BRCA gene mutation	81 (19.6%)	8 (47.1%)	0.01	3.64
Bilateral reconstruction	152 (36.8%)	10 (58.8%)	0.08	2.45
Malignancy present at time of surgery	156 (38.0%)	4 (23.5%)	0.31	0.50
Adjuvant therapy (chemotherapy, hormonal therapy, radiotherapy)	174 (42.1%)	8 (47.1%)	0.80	1.22
Postoperative radiotherapy	115 (27.8%)	6 (35.3%)	0.58	1.41
Chemotherapy	183 (44.3%)	7 (41.2%)	1.00	0.88
Hormonal therapy	112 (27.1%)	4 (23.5%)	1.00	0.83
DIEP flap breast reconstruction‡	389 (94.2%)	17 (100%)	0.61	NA
Primary reconstruction	113 (27.4%)	7 (41.2%)		
Secondary reconstruction	269 (65.1%)	9 (52.9%)	0.46	
Combined reconstruction§	31 (7.5%)	1 (5.9%)		
Previous thromboembolic events	4 (1.0%)	0 (0%)	1.00	NA
Mechanical prophylaxis	345 (83.5%)	13 (76.5%)	0.50	0.64
Pneumatic stockings	91 (22.0%)	2 (11.8%)	0.55	0.47
A-V Impulse System foot pumps	104 (25.2%)	6 (35.3%)	0.40	1.62
Elastic stockings	150 (36.3%)	5 (29.4%)	0.62	0.73

SPE, symptomatic pulmonary embolism; BMI, body mass index; NA, not applicable.
*Adjusted standardized residuals were evaluated as *Z* scores.
†Fisher's exact test.
‡All cases with symptomatic pulmonary embolism underwent DIEP flap breast reconstruction.
§Combination of primary and secondary reconstruction.

Body Mass Index

Obesity is a known risk factor for pulmonary embolism.[26] Several theories have emerged explaining the link between obesity and the increased risk of pulmonary embolism, including induced blood clotting by leptin, a hormone released by fat cells,[27] a rise in estrogen and progesterone levels,[28,29] and progressive atherosclerosis.[30,31]

We found a significantly higher body mass index in the symptomatic pulmonary embolism group (29.8 kg/m²) than in the non–symptomatic pulmonary embolism group (26.7 kg/m²). In contrast, not a single case of symptomatic pulmonary embolism occurred after abdominal flap breast reconstruction in a recent series of 25 women with a body mass index greater than 40 kg/m².[32] The authors used low-molecular-weight heparin and applied pneumatic stockings. However, in their series, there was a trend toward performing muscle-sparing free TRAM flaps, which may explain the relatively short operation duration for both unilateral and bilateral breast reconstructions, averaging 360 and 500 minutes, respectively. In our series, the average operation duration was 402 minutes for unilateral and 600 minutes for bilateral breast reconstruction. Also, the low number of patients in the previous study is likely to preclude accurate risk estimation.

Table 5. Result of Backward Logistic Regression Analysis*

	Estimate	SE	*p*	Odds Ratio (95% CI)
BMI	0.168	0.06	0.005	1.18 (1.05–1.33)
BRCA	1.082	0.513	0.035	2.95 (1.08–8.06)
Constant	−8.288	1.789	<0.001	

BMI, body mass index; *BRCA*, breast cancer gene mutation.
*Nagelkerke's $R^2 = 0.110$ and Cox and Snell $R^2 = 0.032$.

General Anesthesia and Operation Duration

Prolonged general anesthesia time is a known risk factor for deep venous thrombosis.[11,33–35] In our series, total anesthesia time averaged 7.9 hours in the non–symptomatic pulmonary embolism group and 9.0 hours in the symptomatic pulmonary embolism group, although this difference did not reach statistical significance ($p = 0.07$). The same was true for bilateral reconstructions that have longer operative times; we found a nonsignificant trend for its effect on the risk of symptomatic pulmonary embolism ($p = 0.08$). In the *multivariate* backward logistic regression analysis, only body mass index and *BRCA* remained significant predictors for symptomatic pulmonary embolism because of their stronger effects. In this analysis, operation duration and bilaterality were not

Table 6. Cutoff Scores, Sensitivity, Specificity, False-Positives, and Area under the Curve

Model	Cutoff	Sensitivity (%)	Specificity (%)	Overall Accuracy (%)	AUC
1. Most efficient					
BRCA +	≥1	100	30	33	0.650
BMI >25 +	≥2	100	63	64	0.814
BMI >28	≥3	29	92	89	0.605
2. Second best					
BRCA +	≥1	100	23	27	0.617
BMI >24 +	≥2	100	51	53	0.753
BMI >27 +	≥3	65	75	75	0.700
BMI >30	≥4	24	94	91	0.587
3. WHO cutoff					
BRCA +	≥1	100	30	33	0.650
BMI >25 +	≥2	76	72	73	0.744
BMI >30	≥3	24	94	91	0.587

BMI, body mass index; *BRCA*, breast cancer gene mutation; AUC, area under the curve; WHO, World Health Organization.

significant predictors, possibly because of their multicollinearity with *BRCA*.

BRCA Mutations and Malignancy

Cancer cells exert a procoagulant activity in their microenvironment that can extend systemically.[36,37] The literature is increasingly supporting the idea that genetic mutations responsible for malignant transformation also influence genes that control hemostasis. Activation of hemostasis provides cancer cells with a fibrin scaffold that is beneficial for tumor growth and invasion. In addition, tumor progression is stimulated by signaling effects of factors such as tissue factor, plasminogen activator inhibitor-1, or cyclooxygenase-2, which control invasive growth, protection from apoptosis, and angiogenesis.[38] Cancer-specific therapies such as chemotherapy, hormonal therapy, and radiotherapy, although often indispensable, constitute additional risk factors for venous thromboembolism.[15] In our study, the presence of malignancy, as in primary breast reconstruction after therapeutic mastectomy, did not significantly increase the risk for symptomatic pulmonary embolism, nor did the

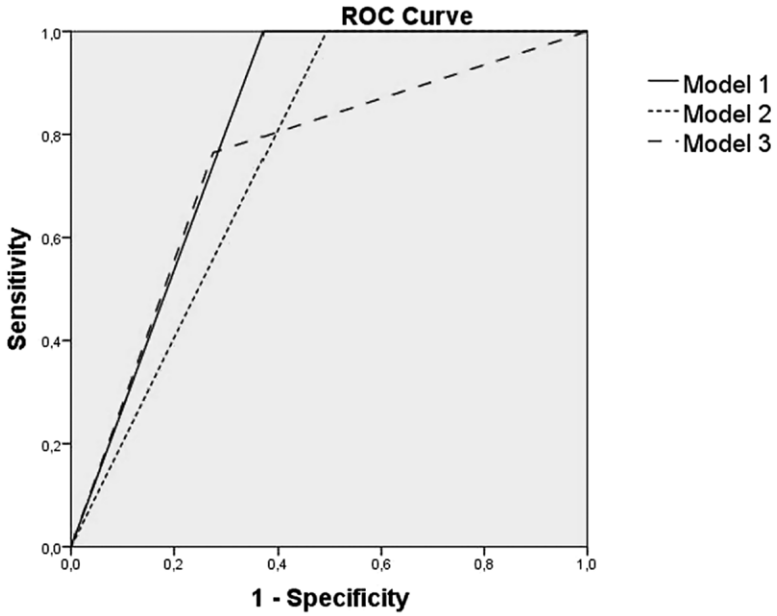

Fig. 1. Receiver operating characteristic (*ROC*) curves of selected models. *BRCA*, breast cancer gene mutation; *BMI*, body mass index; *AUC*, area under the curve; *WHO*, World Health Organization.

application of chemotherapy, hormone therapy, or radiotherapy (Tables 3 and 4). Of note, the majority of our population had early-stage breast cancer. As such, the relative contribution of malignancy to symptomatic pulmonary embolism may have been limited.

Fisher's exact test showed a significantly higher risk of symptomatic pulmonary embolism in patients with a *BRCA* mutation ($p = 0.01$). Almost all patients with a positive *BRCA* status underwent bilateral reconstruction, which is associated with a significantly longer operation duration compared with unilateral reconstruction. The significantly higher operation duration does not contribute to the increased risk of symptomatic pulmonary embolism by itself, which can be concluded from the backward logistic regression analysis. After removing the nonsignificant operation duration effect from the model, it was revealed that a positive *BRCA* status is an independent risk factor for symptomatic pulmonary embolism.

Discrepancy in Risk of Symptomatic Pulmonary Embolism between Abdominal Flap Breast Reconstruction and Head and Neck Reconstruction

Generally, patients undergoing head and neck reconstructive surgery have more risk factors for symptomatic pulmonary embolism than abdominal flap breast reconstruction patients. Patients undergoing head and neck surgery are generally older, and in nearly all cases cancer is present at the time of surgery. They too are often exposed to radiotherapy, chemotherapy, and lengthy reconstructive procedures with autologous free tissue transplants. Many patients undergoing head and neck reconstructive surgery have a history of excessive smoking, which causes additional comorbidities, predisposing them to venous thromboembolism. Nevertheless, the literature reports markedly lower rates of venous thromboembolism in patients undergoing head and neck reconstructive surgery compared with patients with abdominal flap breast reconstruction.[39] A relatively high body mass index in abdominal flap breast reconstruction patients compared with head and neck patients partially explains this discrepancy.

Also, the use of abdominal flaps may render a higher risk for venous thromboembolism compared with flaps harvested from other regions. Tightening of the abdominal wall after flap harvest increases abdominal pressure and thereby reduces venous return. The effects of increased intraabdominal pressure include stasis in the iliac veins and reduced flow through the proximal femoral veins, with a subsequent increase in intravenous pressure and increased diameter of the proximal femoral veins.[40] The necessity to position and nurse patients in a Fowler's position during the initial postoperative phase could cause additional pooling of blood in the venous system of the lower extremities. Furthermore, discontinuation of the superficial abdominal veins as a result of abdominal flap harvest could disrupt venous return in the abdomen, with possible implications for the deeper venous circulation. Finally, although oncogenes responsible for head and neck malignancies, such as epidermal growth factor receptor variant III mutations, are known to up-regulate tissue factor and initiate coagulation,[38] they might be less prone to causing systemic coagulopathy compared with *BRCA* gene mutations.

The Davison-Caprini Risk-Assessment Model has been validated in a general plastic surgery population, with the main inclusion criteria being surgery under general anesthesia and postoperative hospital admission.[19] Patients who received chemical thromboprophylaxis were excluded.[19] These criteria are too generic in nature, and therefore this risk-assessment model is unlikely to be suitable for accurate prediction of symptomatic pulmonary embolism after abdominal flap breast reconstruction. We developed a more specific model and determined the optimal specificity and sensitivity at different cutoff scores (Table 6). Using model 1, patients with a score of 2 or higher are at increased risk for symptomatic pulmonary embolism. These patients could possibly benefit from a stronger thromboprophylaxis approach, such as an increased dosage of low-molecular-weight heparin. In case of *BRCA*-positive patients undergoing bilateral reconstruction, a body mass index exceeding 28 would indicate a very high risk for symptomatic pulmonary embolism. These patients should be explicitly warned about the risk of symptomatic pulmonary embolism after abdominal flap breast reconstruction. If other risk factors are also present (e.g., hereditary predisposition to venous thromboembolism), the reconstructive surgeon should strongly consider negative advice for abdominal flap breast reconstruction.

As yet, we have not applied our prediction model in our own clinical practice and therefore cannot present any preliminary data. The data in this study are purely informational, and the presented model needs further clinical validation. However, to reduce the risk of thromboembolic complications, we have stopped operating on

patients with a body mass index exceeding 35 kg/m^2. To reduce the risk of flap-related complications in obese patients, we liberally include two or more perforators or perform a muscle-sparing TRAM flap. Finally, patients must have stopped smoking at least 6 weeks preoperatively.

The present study was a first effort for constructing a screening tool specifically for symptomatic pulmonary embolism after abdominal flap breast reconstruction. Although the total sample included a reasonable number of participants, the statistical power was reduced by a limited number of patients with pulmonary embolism. A power calculation using the procedure described by Buderer,[41] with an acceptably judged sensitivity range of 80 to 100 percent, a specificity range of 70 to 90 percent, and a proportion of symptomatic pulmonary embolism of 4 percent, pointed out that 875 participants were needed. Future research, with the inclusion of more patients with pulmonary embolism, can refine our presented screening tool and can increase the sensitivity and specificity of this instrument. In addition, the role of *BRCA* gene mutations in systemic coagulopathy is an interesting topic for future investigation.

CONCLUSIONS

The rate of symptomatic pulmonary embolism was 4.0 percent, despite standard thromboprophylaxis. Body mass index and *BRCA* mutation were significant predictors for symptomatic pulmonary embolism. We integrated these factors into a prediction model that provides a useful tool for identification of high-risk patients. This category may benefit from a more aggressive thromboprophylaxis approach.

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