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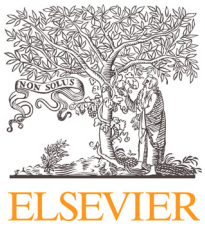

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Nation-wide validation of a multicenter risk model for implant loss following implant-based breast reconstruction

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Implant-based breast reconstruction;
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Summary *Introduction:* Implant loss following breast reconstruction is a devastating complication, which should be prevented as much as possible. This study aimed to validate a previously developed multicenter risk model for implant loss after implant-based breast reconstructions, using national data from the Dutch Breast Implant Registry (DBIR).
Methods: The validation cohort consisted of patients who underwent a mastectomy followed by either a direct-to-implant (DTI) or two-stage breast reconstruction between September 2017 and January 2021 registered in the DBIR. Reconstructions with an autologous adjunctive and patients with missing data on the risk factors extracted from the multicenter risk model (obesity, smoking, nipple preserving procedure, DTI reconstruction) were excluded. The primary outcome was implant loss. The predicted probability of implant loss was calculated using beta regression coefficients extracted from the multicenter risk model and compared to the observed probability.
Results: The validation cohort consisted of 3769 reconstructions and implant loss occurred after 307 reconstructions (8.1%). Although the observed implant loss rate increased when the risk factors accumulated, the predicted and observed probabilities of implant loss did not match. Of

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the four risk factors in the multicenter risk model, only obesity and smoking were significantly associated to implant loss.
Conclusion: The multicenter risk model could not be validated using nationwide data of the DBIR and is therefore not accurate in Dutch practice. In the future, the risk model should be improved by including other factors to provide a validated tool for the preoperative risk assessment of implant loss.

Introduction

Implant loss is the most severe complication following implant-based breast reconstruction. It has a major impact on the patient's life, both physically and emotionally.[1] Re-operations associated with implant loss may result in a significant decrease in patient satisfaction and in a substantial increase in hospital costs. In addition, it could lead to a delay in further adjuvant treatment.[2–6]

According to the literature, the occurrence of implant loss varies from 1.8% to 16.9%. Several risk factors for implant loss have been described over the years, including radiotherapy, obesity, smoking, higher age, and direct-to-implant (DTI) reconstruction.[3,7,8] Recently, a risk model to improve patient information and decision making for the type of mastectomy and reconstruction was developed by our study group. However, this model was derived from retrospective data obtained in two medical centers, so the findings may not be generalizable to the reconstructive population at large.[9]

Therefore, a nationwide population-based cohort with data from the Dutch Breast Implant Registry (DBIR) was used to validate our multicenter risk model for implant loss after implant-based breast reconstructions for mastectomy.[10,11] The aims were to improve patient information on the risk of implant loss and its risk factors, and to improve decision making for the type of mastectomy and reconstruction.

Methods

Study design

For this nationwide population-based validation study, data were extracted from the DBIR, which is a national, prospective, opt-out registry, with mandatory registration of all breast implant surgery performed in The Netherlands.[12] All breast implants (tissue expanders (TE) and permanent implants) used for reconstructive or cosmetic purposes in the Netherlands are registered in the DBIR. The DBIR started in 2015, and all Dutch hospitals that perform breast implant reconstructions participate in this registry.[12] The multicenter risk model was extracted from our recently published study.[9] The study protocol was approved by the scientific committee of the DBIR. No informed consent or ethical approval was required. The study was conducted in accordance with the Declaration of Helsinki and reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[13,14]

Validation cohort

Patients who underwent a mastectomy for any reason followed by either a two-stage or a DTI breast reconstruction between September 2017 and January 2021 were identified from the DBIR. Patients in whom an autologous adjunctive reconstruction was used and patients with missing data on the variables of the multicenter risk model were excluded.

Multicenter risk model

Data from the multicenter risk model for implant loss were extracted and used in this study for validation of the results. Details on methods, results and conclusions were published previously.[9] In short, 297 breasts in 225 patients were evaluated after implant-based breast reconstruction. The occurrence of implant loss was 11.8%. A risk model was created that identified the following risk factors for implant loss: obesity (defined as body mass index (BMI) >30 kg/m^2), active smoking status, nipple sparing procedure, and a DTI approach. The corresponding beta regression coefficients and odds ratios were extracted and are depicted in Table 1. The predicted implant loss risk ranged from 3.6% to 78.2% in patients with zero to four risk factors.[9]

Outcome measures and definitions

The primary outcome was implant loss due to a wound healing-related complication. The following outcomes available in the DBIR were considered as implant loss: (1) explantation of TE or permanent implant because of flap problems, infection, skin necrosis, hematoma, seroma or when no reason was provided; (2) planned replacement of TE with permanent implant combined with flap problems, infection, and skin necrosis; (3) unplanned replacement of TE with permanent implant because of flap problems, infection, skin necrosis, hematoma, or seroma; (4) replacement of TE or permanent implant with TE because of flap problems, infection, skin necrosis, hematoma, seroma, or when no reason was provided; (5) replacement of TE or permanent implant with autologous tissue combined with flap problems, infection, or skin necrosis; (6) replacement of permanent implant with permanent implant because of flap problems, infection, skin necrosis, hematoma, or seroma. The following indications for explantation or revision were not considered as implant loss due to a wound healing-related complication: dissatisfaction with size, asymmetry, breast pain,

Table 1 Data from multicenter risk model.

Risk factors	Beta regression	OR	*P*-value
Obesity	1.381	1	
		2.877 (1.299–6.376)	*0.009*
Active smoking	1.172	1	*0.003*
		3.280 (1.498–7.181)	
Nipple preserving	1.110	1	*0.003*
		3.081 (1.460–6.502)	
Reconstruction type	0.902	1	*0.003*
		3.130 (1.483–6.610)	
Constant	−3.286		

The four risk factors in the multicenter risk model and corresponding beta regression coefficients. ORs and *P*-values are presented. OR indicates odds ratio, significant *P*-values are noted in italic.

autoimmune syndrome induced by adjuvants (ASIA), suspected anaplastic large cell lymphoma (ALCL), newly diagnosed breast cancer, device malposition, scarring, capsular contracture, or device rupture. The following incision sites available in the DBIR were considered as nipple preserving procedures: mastectomy scar (nipple sparing), inframammary, periareolar and axillary incisions. Mastectomy scar (general) was interpreted as not nipple sparing.

Statistical analysis

Categorical variables were depicted as frequencies with percentages, and continuous variables are presented as mean with standard deviations (SD) or median with interquartile range (IQR) based on the distribution. Differences in baseline characteristics between groups were tested with unpaired T test, Mann-Whitney U test, or chi-square tests. To assess the validity of the local risk model, the beta regression coefficients listed in Table 1 were used to calculate the predicted probability of implant loss in the validation cohort. For each predicted probability group, the observed probability, with corresponding SD, was calculated. This was visualized in a calibration plot, with predicted probability on the y-axis and observed probability on the x-axis. Finally, univariate logistic regression was performed to determine the association between risk factors and implant loss in the current cohort, providing odds ratios (OR) with 95% confidence intervals (CI) and *P*-values. IBM SPSS statistics (version 26) was used for statistical analysis, and a *P*-value <0.05 was considered statistically significant.

Results

Validation study population

A total of 9373 implant-based breast reconstructions were registered in the DBIR between inception and January 2021; 6194 reconstructions were registered during the study period. After exclusion of patients in whom autologous adjunctive procedures were used, 5699 reconstructions remained. To validate the previously described risk model, 1930 patients were excluded because data of one or more risk factors was missing, resulting in a total of 3769 reconstructions. The mean age in this cohort of 3769 reconstructions was 48.8 ± 11.3 years, with a mean BMI of 24.7 ± 4.2 kg/m^2. Patient selection and distribution are visualized in a flowchart in Fig. 1. The baseline characteristics of the validation study population were compared to the baseline characteristics of the previous multicenter risk model population (Table 2).

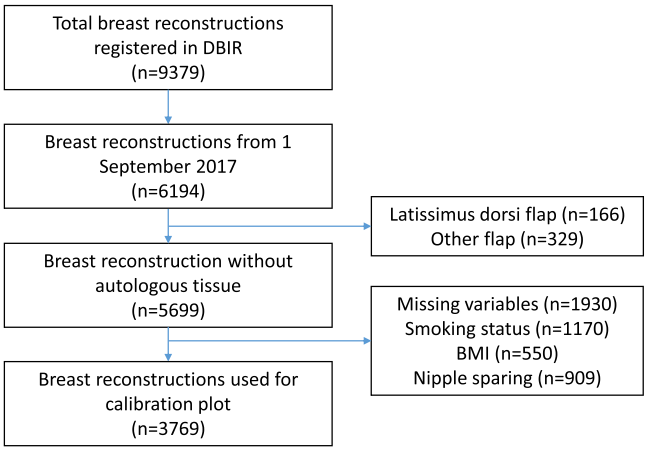

Figure 1 Flowchart of in- and excluded patients.

Risk model validation

The validation cohort consisted of 3769 reconstructions and implant loss occurred after 307 reconstructions (8.1%). Patient and surgery characteristics stratified for implant loss are summarized in Table 3. There were active smokers in 486 (12.9%) reconstructions and obese patients (BMI>30) in 401 (10.6%) reconstructions. A nipple sparing procedure was performed in 1126 (29.9%) reconstructions, and a definite implant was directly placed in 832 (22.1%) reconstructions. This resulted in no risk factors for 1764 reconstructions, one risk factor for 1480 reconstructions, two risk factors for 485 reconstructions, three risk factors for 39 reconstructions, and four risk factors for one reconstruction. The observed implant loss rates for each number of risk factors are presented in Table 4. The predicted probabilities for each risk factor combination were extracted and compared to the observed probabilities of the validation cohort. This comparison was visualized in a calibration plot (Fig. 2). A substantial

Table 2 Baseline comparison between cohorts.

Baseline characteristics	Validation cohort ($n = 3769$)	Multicenter cohort ($n = 297$)	P-value*
Age, years	48.8 ± 11.3	47.5 ± 11.3	0.068
BMI, L^2/m	24.7 ± 4.2	25.3 ± 4.8	*0.033*
Obesity	401 (10.6)	47 (15.8)	*0.006*
ASA score			*<0.001*
I	1919 (51.3)	75 (25.3)	
II	1652 (44.2)	203 (68.4)	
III	169 (4.5)	18 (6.1)	
IV	0 (0)	1 (0.3)	
Missing	29	0	
Current smoker	486 (12.9)	47 (16.2)	0.108
Missing	0	7	
Indication			*<0.001*
Breast cancer	3064 (81.3)	211 (71.0)	
Prophylactic	705 (18.7)	86 (29.0)	
Type reconstruction			0.453
Permanent implant	832 (22.1)	60 (20.2)	
Tissue expander	2937 (77.9)	237 (79.8)	
Nipple preserving	1126 (29.9)	119 (40.5)	*<0.001*
Missing	0	3	
Volume permanent implant	388 (295-480)	413 (305-515)	*0.007*
Volume tissue expander			*<0.001*
<100	848 (30.2)	68 (28.8)	
100-200	1677 (59.7)	114 (48.3)	
>200	285 (10.1)	54 (22.9)	
Missing	127	1	

Baseline characteristics of the validation cohort compared to the baseline characteristics of the previous multicenter cohort.

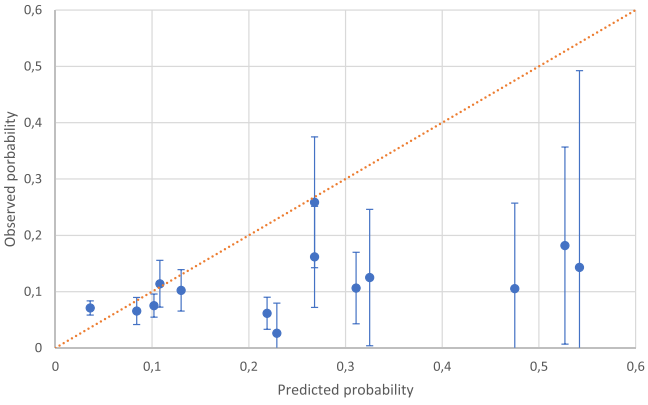

Figure 2 Calibration plot. Ratio between the predicted probability on implant loss based on the previous risk model and the observed probability in the current cohort.

agreement in probabilities was observed from 0.0 to 0.13 as the reference line lies within the CI of four out of five data points. However, the rest of the predicted and observed probabilities did not match, indicating a poor agreement.

Association between risk factors and implant loss in current cohort

The associations between risk factors and implant loss were determined in the current cohort using univariable logistic regression. Obesity and active smoking status were significantly associated with implant loss (OR: 1.499 (1.072-2.094), $P = 0.019$ and OR: 1.772 (1.315-2.387), $P<0.001$, respectively). A nipple preserving procedure and DTI reconstruction were not significantly related to implant loss (OR: 1.005 (0.799-1.295), $P = 0.971$ and OR: 0.984 (0.742-1.305), $P = 0.984$, respectively). These results are summarized in Table 5.

Discussion

This study aimed to validate a multicenter risk model for implant loss after implant-based breast reconstructions, using the DBIR database. Although the observed implant loss rate increased when the risk factors accumulated, the calibration plot showed that the predicted probability of implant loss based on the previous risk model and the observed probability in the current nationwide cohort do not match. This implies that the previous created risk model is not generalizable to the reconstructive population at large.

It is crucial that any developed model is generalizable and predicts well in 'comparable but different' patients outside the development set.[15] In the current validation cohort, an implant loss rate of 8.1% was found after implant-based breast reconstruction, which is slightly lower than the 11.8% implant loss rate found in the original cohort. The previous risk model consists of four risk factors: obesity, active smoking status, a nipple sparing procedure, and a DTI approach. BMI, smoking status, and a DTI approach could

Table 3 Validation cohort.

Baseline characteristics	No implant loss ($n = 3462$)	Implant loss ($n = 307$)	*P*-value*
Age, years	48.7 ± 11.4	50.3 ± 10.3	*0.007*
BMI, L^2/m	24.6 ± 4.2	25.6 ± 4.7	*<0.001*
Obesity	356 (10.3)	45 (11.2)	*0.017*
ASA score			0.112
I	1775 (51.7)	144 (47.4)	
II	1512 (44.0)	140 (46.1)	
III	149 (4.3)	20 (6.6)	
Missing	26	3	
Current smoker	425 (12.3)	61 (19.9)	*<0.001*
Indication			0.081
Breast cancer	2803 (81.0)	261 (85.0)	
Prophylactic	659 (19.0)	46 (15.0)	
Neoadjuvant radiotherapy	155 (4.5)	24 (7.8)	*0.009*
Missing	19	0	
Preoperative antibiotics	3341 (96.8)	297 (97.1)	0.794
Missing	10	1	
Antiseptic rinse	3169 (91.9)	273 (88.9)	0.070
Missing	14	0	
Kellerfunnel	329 (9.6)	33 (10.7)	0.495
Missing	17	0	
Nippleguards	1001 (29.0)	85 (27.7)	0.617
Missing	15	0	
Type reconstruction			0.912
Permanent implant	765 (22.1)	67 (21.8)	
Tissue expander	2697 (77.9)	240 (78.2)	
Nipple preserving	1034 (29.9)	92 (30.0)	0.971
PM cover	3134 (91.1)	264 (86.3)	*0.001*
Missing	21	1	
Mastopexy	69 (2.0)	9 (2.9)	0.271
Missing	20	1	
Drains	3304 (95.5)	293 (95.4)	0.949
Missing	3	0	
Volume permanent implant	375 (290–475)	420 (340–535)	0.344
Volume tissue expander			0.167
<100	777 (30.2)	71 (30.2)	
100–200	1545 (60.0)	132 (56.2)	
>200	253 (9.8)	32 (13.6)	
Missing	122	5	
Adjuvant radiotherapy	182 (6.7)	22 (8.5)	0.267
Missing	746	49	
Postoperative antibiotics	2015 (58.5)	176 (57.7)	0.776
Missing	20	2	

Baseline characteristics of the validation cohort and stratified for implant loss.
Data are n (%), mean ± SD or median (IQR). Significant *P*-values are denoted in italic. ASA indicates American Association of Anesthesiologists; BMI, body mass index, PM; pectoralis major.

Table 4 Validation of risk model.

Risk factors	Reconstructions	Implant loss
0	1491	114 (7.1)
1	1413	128 (8.3)
2	508	58 (10.2)
3	49	7 (12.5)
4	1	0 (0.0)

Accumulating number of risk factors and corresponding observed implant loss rates.

directly be extracted from the DBIR data. However, a nipple sparing procedure was not an exact variable in the DBIR database and could only be derived from the incision type. Furthermore, substantial differences in baseline characteristics were observed between the validation cohort and previous multicenter cohort. Next to ASA score, indication for surgery, permanent implant volume and TE volume, the rate of nipple sparing reconstructions was significantly lower in the validation cohort compared to the multicenter cohort (29.9% vs. 40.5%, respectively). Furthermore, the incidence of obesity was significantly lower in the validation cohort

Table 5 Risk factors in current cohort Association between risk factors and implant loss in current cohort using univariable logistic regression.

Risk factors	Group	Event rate (%)	OR	*P*-value
Obesity	BMI <30	7.8	1	*0.018*
	BMI >30	11.2	1.499 (1.072-2.094)	
Active smoking	No	7.5	1	*<0.001*
	Yes	12.6	1.772 (1.315-2.387)	
Nipple preserving	No	8.1	1	0.971
	Yes	8.2	1.005 (0.799-1.295)	
Reconstruction type	TE	8.2	1	0.984
	Prosthesis	8.1	0.984 (0.742-1.305)	

Event rate describes the rate of implant loss in breast reconstructions with and without the risk factor. BMI indicates body mass index; OR, odds ratio; TE, tissue expander. Significant *P*-value noted in italic.

(10.6% vs. 15.8%). The other risk factors were not significantly different between the two cohorts.

A nipple sparing procedure and a DTI approach were not significantly associated to implant loss in the current validation cohort. Since these factors represented half of the risk model, it is understandable that the risk model was not accurate in the current validation cohort. It could be hypothesized that the risk of implant loss increases in a nipple sparing procedure as wound problems or necrosis seem to be most common in the nipple area. However, to date, a nipple sparing procedure has not been described as a risk factor for implant loss, thereby confirming the results of this validation cohort. In addition, a DTI approach is a frequently described risk factor for implant loss,[3] but this was not observed in the current validation cohort. However, the literature is contradictory on this topic, and critical patient selection, for instance by judgment of mastectomy flap tissue quality, is an important component.[16-18]

Although the current study contained a large sample size with data of a nationwide population, this database study has certain limitations. First of all, the accuracy of all DBIR data could not be confirmed due to its anonymized nature and privacy regulations. Another limitation is the restriction to the data collected in the database. One of the risk factors in the multicenter risk model was a nipple sparing procedure, which was not a direct variable in the DBIR database. However, this factor could be indirectly derived from the variable 'incision site'. The same applied to the definition of implant loss, which was created based on the available data in the DBIR database. However, the accuracy of these definitions could not be confirmed due to privacy regulations within the anonymized data. Finally, the registration of explantations might be an underestimation of the clinical practice due to under registration.

In conclusion, the observed incidence of implant loss in the validation cohort was 8.1%, and does increase if the number of risk factors accumulates. However, the predicted probability of implant loss based on the multicenter risk model did not match the observed probability in the current nationwide cohort, indicating that the multicenter risk model is not accurate in Dutch practice. In the future, attempts will be made to improve the risk model and provide a validated tool for the risk assessment of implant loss. This could lead to improved pre-operative information for patients, and the ultimate goal to decrease the risk of implant loss by optimizing the surgical strategy in a personalized fashion.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.08.065.

References

1. Kouwenberg CAE, van Hoogdalem LE, Mureau MAM, et al. Patients' and surgeons' experiences after failed breast reconstruction: a qualitative study. *J Plast Reconstr Aesthet Surg* 2021;**74**:1480-5.
2. Darragh L, Robb A, Hardie CM, et al. Reducing implant loss rates in immediate breast reconstructions. *Breast* 2017;**31**:208-13.
3. Fischer JP, Wes AM, Tuggle CT 3rd, Serletti JM, Wu LC. Risk analysis of early implant loss after immediate breast reconstruction: a review of 14,585 patients. *J Am Coll Surg* 2013;**217**:983-90.
4. Knight HJ, Musgrove JJ, Youssef MMG, et al. Significantly reducing implant loss rates in immediate implant-based breast reconstruction: a protocol and completed audit of quality assurance. *J Plast Reconstr Aesthet Surg* 2020;**73**:1043-9.
5. Ozturk CN, Ozturk C, Soucise A, et al. Expander/Implant removal after breast reconstruction: analysis of risk factors and timeline. *Aesthetic Plast Surg* 2018;**42**:64-72.
6. Sue GR, Sun BJ, Lee GK. Complications after two-stage expander implant breast reconstruction requiring reoper-

ation: a critical analysis of outcomes. *Ann Plast Surg* 2018;**80**:S292–SS94.
7. Hirsch EM, Seth AK, Kim JYS, et al. Analysis of risk factors for complications in expander/implant breast reconstruction by stage of reconstruction. *Plast Reconstr Surg* 2014;**134** 692e–699e.
8. Becherer BE, Young-Afat HE, Vrancken DA, Peeters MTFD, Rakhorst HA, Mureau MAM. Revision incidence after immediate direct-to-implant versus two-stage implant-based breast reconstruction: results from a nationwide breast implant registry. *Plast Reconstr Surg* 2022.
9. Blok YL, van Lierop E, Plat VD, et al. Implant loss and associated risk factors following implant-based breast reconstructions. *Plast Reconstr Surg Glob Open* 2021;**9**:e3708.
10. Rakhorst HA, Mureau MAM, Cooter RD, et al. The new opt-out Dutch National Breast Implant Registry - lessons learnt from the road to implementation. *J Plast Reconstr Aesthet Surg* 2017;**70**:1354–60.
11. Spronk PER, Becherer BE, Hommes J, et al. How to improve patient safety and quality of care in breast implant surgery? First outcomes from the Dutch Breast Implant Registry (2015-2017). *J Plast Reconstr Aesthet Surg* 2019;**72**:1607–15.
12. Barati N, Vrolijk JJ, Becherer BE, et al. Using a digital implant catalog improves data quality and reduces administrative burden in the Dutch breast implant registry. *Aesthet Surg J* 2021.
13. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bmj* 2007;**335**:806–8.
14. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;**310**:2191–4.
15. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart* 2012;**98**:691–8.
16. Azouz V, Lopez S, Wagner DS. Surgeon-controlled comparison of direct-to-implant and 2-stage tissue expander-implant immediate breast reconstruction outcomes. *Ann Plast Surg* 2018;**80**:212–16.
17. Srinivasa DR, Garvey PB, Qi J, et al. Direct-to-implant versus two-stage tissue expander/implant reconstruction: 2-year risks and patient-reported outcomes from a prospective, multicenter study. *Plast Reconstr Surg* 2017;**140**:869–77.
18. Basta MN, Gerety PA, Serletti JM, Kovach SJ, Fischer JP. A systematic review and head-to-head meta-analysis of outcomes following direct-to-implant versus conventional two-stage implant reconstruction. *Plast Reconstr Surg* 2015;**136**:1135–44.