Present and Future of Machine Learning in Breast Surgery: a systematic review

(Running Head: Machine Learning in Breast Surgery)

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Abstract:

Background: Machine learning (ML) is a set of models and methods that can automatically detect patterns in vast amounts of data, extract information and use it to perform decision making under uncertain conditions. The potential of ML is significant, and breast surgeons must strive to be informed with the up-to-date knowledge and its applications. Here, we aim to review the current applications of ML in breast surgery.

Methods: A systematic database search was conducted of original articles that explored the use of ML and/or AI in breast surgery in EMBASE, MEDLINE, Cochrane database and Google Scholar, from inception to December 2021.

Results: Our search yielded 477 articles, of which 14 studies were included in this review, featuring 73,847 patients. Four main areas of application were identified: 1) ML for predictive modelling of breast surgical outcomes; 2) ML in breast image-based context for analysis and detection, including mammography; 3) ML within screening and triaging of breast surgery patients; 4) ML network utility for detective purposes. There is evident value to the use of ML in pre-operative planning and provision of information for breast surgery in a cancer and an aesthetic context. ML outperformed traditional statistical modelling in all studies for predicting mortality, morbidity, and quality of life outcomes. ML patterns and associations could support planning, anatomical visualisation, and surgical navigation.

Conclusion: ML demonstrated promising applications for improving breast surgery outcomes and patient-centred care, nevertheless, there remain important limitations and ethical concerns relating to implementing AI into everyday surgical practices.

Background:

Artificial intelligence (AI) refers to computer systems that mimic human cognitive functions and learn using large data sets. (1) Recent years have shown a dramatic development in these technologies in healthcare employed in a wide variety of diagnostic and decision-making processes. (2) In an emerging era of big data, the scope and scale of patient data available and leaps in computational ability has allowed AI to develop and improve in its efficiency and applicability. (3)

AI technology is progressing rapidly with support from healthcare professionals, industry and governments. (4) Healthcare has adopted these technologies to improve patient outcomes, especially in the field of surgery. These technologies demonstrate unique potential in breast surgery: pre-operative planning, patient outcome predictions, and even overcoming the challenges of the COVID-19 pandemic as demonstrated by the recent COVIDSurg Collaborative study that addressed the impact of COVID-19 on patient mortality with a predictive model. (5)

AI encompasses many disciplines of computer learning, and clinically relevant subtypes of AI include machine learning (ML). (1,6) Machine learning is a subset of this field where a system focuses on using algorithmic packages and data to mimic the way humans learn. (2) The algorithms use data inputs to 'learn', uncovering associations in data sets via pattern recognition, repetition and modification to make autonomous decisions and predict future outcomes. Common subsets of ML include prediction models, deep learning and natural language processing. (7-8)

Breast surgery, a sub-speciality within general surgery, is a field that has much to benefit from the advances in AI to provide the best patient care by surgical interventions in benign and malignant breast disease. ML in breast surgery may involve these sets of models and methods to detect patterns in vast amounts of patient data, extract appropriate information and use it to perform decision making under uncertain conditions. (9) From supporting pre-operative planning to predicting future outcomes of surgery. The potential applications of ML is significant, and breast surgeons must strive to be informed with the up-to-date knowledge and applications of this subset of AI within the speciality. (10-11)

The aim of this review is to study the applications of ML in breast surgery. Past reviews in other surgical specialities have been written, but none specifically for breast surgery. This review is designed to closely evaluate the current applications by synthesising current research, and to catalyse future research efforts into this advancing field.

Methods

Literature Search Strategy

This systematic review was conducted in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was conducted including EMBASE, MEDLINE, Cochrane, PubMed and Google Scholar from inception to December 2021 (*Figure 1).* The search terms used were (Machine Learning OR Artificial Intelligence OR Deep learning OR Decision Trees OR Neural Networks) AND (Breast Surgery OR Mastectomy OR Breast-conservative Surgery OR Breast reduction OR Breast reconstruction OR Breast augmentation OR Breast Cancer Surgery). Further articles were identified through use of the 'related articles' function on MEDLINE and a manual search of the references lists of articles found through the original search. The only limits used were the English language and the aforementioned time frame.

Study inclusion and exclusion criteria

All original articles were included reporting the use of machine learning in breast surgery. Studies were considered if they presented ML models with the aim of supporting breast surgery or providing a prognosis for an intervention, either used by itself or with other methods. There were no geographical restrictions. Studies were excluded from the review if the quality of available data and data inconsistencies precluded valid extraction or if the study was performed in an animal model. Case reports, reviews, abstracts from meetings and preclinical studies were excluded. Machine learning is a highly erratic and dynamic field – this review contains literature published over a 5-year time period between 2017 and 2021 inclusive, technology has changed significantly even in the five years preceding conduction of this review. As a result, there have been many advancements that have superseded some of the points raised in earlier literature and care was taken to recognise each study in the unique context of its publication year. It was ensured that any outdated findings did not shape the review. By following the aforementioned criteria, two reviewers (C.S and V.S.) independently identified articles for further assessment following title and abstract review. Disagreements between the two reviewers were resolved by a third independent reviewer (A.AR.). Potentially eligible studies were then retrieved for full text assessment.

Data extraction and critical appraisal of evidence

All full texts of retrieved articles were read and reviewed by two authors (C.S. and V.S.) and inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer (A.AR.) made the final decision. Using a pre-established protocol, the following data was extracted: first author, study type and characteristics, number of patients, population demographics, Type of Procedure, Category of machine learning method utilised, Method of machine learning implemented and Main reported outcomes.

Risk of Bias

The risk of bias of the selected articles were evaluated by two independent reviewers (C.S. and V.S.) using an adapted Cochrane Collaboration Risk of Bias tool *(Figure 2)*. The methodological quality of the studies were assessed based of domains: 1. Study Participation, 2. Study Response, 3. Outcome Measurement, 4. Statistical Analysis and Reporting, 5. Study Confounding. An overall grading of low, medium or high risk of bias were then allocated.

Additionally, the limitations of this systematic review have been more expansively outlined in Supplementary File 1.

Results:

Study selection

The literature search identified 477 articles, of which 361 were screened following removal of deduplicates and 24 were full text reviewed and assessed in accordance with the inclusion and exclusion criteria. Following critical appraisal, a total of 14 studies (13-26) were included in this review, featuring 73,847 patients. Figure 1 illustrates the entire study selection process. A summary of the studies collected and their respective designs, type of machine learning mode used and its implementation as well as the main reported outcomes are found in table 1.

There were 9 studies (16-18,20-23,25,26) (5–7,9–12,14,15) which described examples of machine-learning based predictive modelling comprising 45792 patients and included a conglomerate of different modelling methods. Predictive modelling was the use with the most recorded studies and patient volume. The use of ML in imaging is also described. There were 3 studies (13,15,24) (2,4,13) which described examples of machine-learning within an image-based context for analysis and detection comprising 20499 patients – in all cases different modes of machine learning modes were applied. There was a one study (14) (3) which described a case of machine learning's role within screening and triaging – this comprised 7364 patients. There was one study (19) which described a scenario of machine learning network utility for detective purposes – this comprised 355 patients.

(8)

Challenges and recommendations

Figure 3 summarizes the main challenges and respective recommendations developed from the literature with regards to future research being conducted in the field of ML and its application in breast surgery. The recommendations should be taken into the context of each future research study and be considered with all the information available.

Discussion:

This systematic review provides a wide-scope summary of the uses of machine learning and artificial intelligence within breast surgery. Although the review's results demonstrate successes within different approaches in the field, these must be considered in the context of their limitations and recent applications. Most of these applications remain at the 'proof of concept' stage. Healthcare professionals must be prepared to adopt machine learning and artificial intelligence into health practice, as usability and cost-effectiveness of these technologies increase with new developments in the field, and to shape the new landscape in which it is used in medicine. (11)

There is evident value to the use of machine learning in pre-operative planning and provision of information for breast surgery planning in a cancer and an aesthetic context. The diagnosis and detection of pathology is fundamental in pre-operative planning for breast cancer resection. The use of image analysis in clinical applications such as breast imaging, digital pathology and surgical planning has been well-described in the literature. Considering the imaging data available with modern radiology techniques in screening and diagnosis, many machine learning solutions have been derived.

A retrospective image analysis study from Becker et al (13) (2) describes mammography diagnostics using neural network image analysis software that demonstrated the equivalent performance of the neural network with an area under the receiver operating characteristic curve (AUC) of 0.81 and 0.82 respectively in both stages compared to radiologists The results differ between radiologists - however, the neural network showed an increased sensitivity of 72% when compared to a 66.7% average across the radiologists overall. Corroborating these findings, the retrospective simulation study from Dembrower et al (14) (3) and diagnostic study from Buda et al (15)(4) also demonstrate similar levels of prediction using different means of deep learning models such as a commercial artificial intelligence-based cancer-detector algorithm. Cancer detection via datasets allows specific interventions that increase efficiency of operations with the pre-knowledge for surgeons to employ in planning and treatment decisions. The employment of specific machine learning technologies including the Faster-RCNN with Inception-ResNet-v2 deep-learning framework, described in the Yap et al study for a set of ultrasound breast images, facilitates the accurate detection of objects to allow surgeons to focus on the relevant area of the breast (24) (13).

The models that exist can promise a future of reducing the numbers of biopsies and bringing efficiency to radiologist interpretation while reducing workloads. Diagnostic and prognostic applications in imaging and pathology have been studied greatly, with a wide evidence base of applied research. Transfer of imaging information to the operating theatre to more accurately localise cancer to support surgical care can aid the field. Reducing overdiagnosis, morbidity and time efficiency with the efficient use of breast imaging is an aspiration of the future.

Most applications of machine learning within breast surgery, as ascertained by this review, centre around the prediction of patient outcomes prognostically – this is coherent with the wider applications of machine learning within modern surgery (27-29)(16–18). There have been multiple instances, identified across the course of this review, where machine learning was employed alongside traditional statistical modelling for predictive purposes. Indicative of the success of machine learning, the former outperformed the latter in every highlighted example and thus replicates the successes seen across other surgical subspecialties, mostly prominently neurosurgery (30) (19). This is particularly evidenced via the longitudinally-designed Huang et al study which demonstrated that 5-year mortality after breast cancer surgery could be accurately assessed using machine learning algorithms through a variety of input variables (16) (5). Although machine learning packages have been substantiated to show marked improvements to pre-existing models including, but not limited to, least square regression and Cox regression (17,31) (6,20), it must be stated that these still remain limited and relatively novel.

The studies included in this review demonstrated high heterogeneity in the form of machine learning applied within individual cases. In this way, some models have been transparently more consistent and accurate than others. Artificial neural networks, algorithms which have been modelled after the human brain and nervous system and with a basis in the concept of a human neurone (32) (21), have been established as dependable across the scope of this review – exemplified most prominently in the Lou et al. study where the artificial neural network package demonstrated the highest prediction performance index - obtaining a sensitivity of 95.9, specificity of 99.5, PPV of 99.0, NPV of 99.1 and AUC of 97.6 (20) (9). This provides greater support to previous literature which describes the effectiveness of artificial neural networks in other clinical contexts (33-35) (22–24). Artificial neural networks are better adapted to deal with more problematic inputs - specifically, cases where an input may be noisy or incomplete. As a result of these advantages, a 93.75% accuracy rate of identifying a breast cancer patient's post-operative lymphedema status was obtained in the Fu et al. Study (19)(8). Many medical databases, of the scale where a machine learning model can be realistically derived, contain non-normally distributed data. This poses further issue to many forms of modelling which assume a normal distribution within a dataset (23) (12) - as artificial neural networks are applicable to well-correlated data that are not necessarily natively normally distributed, artificial neural networks are more transferrable and can provide greater potential for use in wider treatment contexts beyond breast cancer surgery.

Machine learning's capacity for use in breast surgery can further extend past predicting outcomes and pivot towards providing more holistic patient assessment via the prediction of postsurgical pain, seen in both the Juwara et al (17)(6) and Lotsch et al (18) (7) studies. Machine learning creates opportunities for far more efficient pain assessment that can be undertaken immediately post-operatively, in comparison to pre-existing tools that require time-heavy questionnaires and extensive clinician-patient interaction; this serves great utility in the context of a healthcare system where both time and human resources are often limiting factors. As neuropathic pain can be debilitating for patients, early prediction can allow clinicians to better optimise post-surgical care.

As an additional factor repeatedly indicated via the machine learning models included in this review, a greater surgeon volume was the largest predictor of reduced breast cancer recurrence in patients that had undergone breast cancer surgery (16,20) (5,9). In light of this, there is renewed necessity for machine learning to be implemented to further review the decision-making of surgeons with higher operative volumes. Decision analysis and reinforcement learning, modes of machine learning well-documented within this context (36) (25), would allow this to be paralleled and promote further improvements in decision-making for surgeons with lower operative volumes. This can further minimise postoperative burden. In tandem to this, there has been evidence to suggest that some machine learning packages can outperform even the most experienced surgeons, as determined above, and therefore it may be possible to provide the framework of a specific machine learning package itself as a template for replication by surgeons of all grades.

Additional applications of machine learning on the horizon within the field of breast surgical care can be considered, although most of these remain conceptual. Decision making in modern medicine is complex due to the increasing availability of data to consider before treatment decisions are made (37)(26). Advances in medical knowledge including that of well-researched novel therapies and surgery only dramatically increase the potential treatment choice algorithms. Decision support systems have been well-described, including the DESIREE project (38)(27), that provides breast unit physicians with decision support modules. This is further stipulated in other examples (39) (28) where decision support models regarding recurrence prediction are employed and comprise support systems that encompass artificial intelligence and information visualisation amongst many other technologies.

Computer vision for object and scene recognition could support surgical techniques. Patterns and associations can support planning, anatomical visualisation and surgical navigation. The exploration of machine learning systems that perform or directly complement surgery is rapidly developing, and may be a possibility in the imminent future. Real-time decision making supported by machine learning provides exciting opportunities (40) (29).

The new frontier of surgical innovation, concurrently occurring at the time of the review, is unlike any other observed previously. Despite the benefits and applications in the field as described above, clinicians must be careful to consider the potential limitations and risks of the technology and avoid overt optimism surrounding the capabilities of machine learning, instead focusing realistically on the barriers to its implementation clinically. (41) (30).

Machine learning and artificial intelligence is limited by the lack of accurate and unbiased data collection and input. If data-input bias is evident, predictions may easily become unreliable. Examples include systematic biases due to nonrepresentative predictions for patient groups that are not necessarily represented in research (42) (31). This review does provide evidence in support of theoretical machine learning applications, however, as outlined in a review by Manlhiot et al. (43), care must be taken to recognise that these are not wholly clinically representative. The described machine learning models rely on heavily-curated datasets with relatively few implementation obstacles, in vast contrast to datasets available in clinical practice.

Machine learning can exhibit 'black box' characteristics, with incomprehensibly complex algorithms for their outputs. The learning mechanisms of some machines have been difficult to reproduce, and it has been difficult to justify certain decisions. Measures taken in the programming of these machines to justify decisions and compare with gold standard diagnosis can circumvent this challenge. The challenges surrounding the complexity of machine learning in its current state render it clinically unimplementable without expertise and specialist knowledge - hence, the benefits of it are yet to be properly actioned. Explainable machine learning whereby the system is able to justify how it made its predictions on a level that is comprehensible to a clinician(44,45) (32,33) has come to light as a potential solution to this issue - exemplified in the Moncada-Torres et al study (25) (14) where explainable machine learning consistently outperformed all other methods for predicting outcomes in patients who had undergone breast-conserving surgery or mastectomy. However, this remains one of a set of isolated cases.

In addition, considerations of collaboration with other stakeholders in the implementation of the technology, in order to ensure data is interpreted correctly and applied in the correct manner, should be of paramount importance. These technologies have been criticised due to a lack of confidence regarding their perceived privacy and due to the risk of bias with data collection, as aforementioned Caution and planning to understand the most safe and beneficial method of implementation, via close collaboration of healthcare professionals with machine learning and artificial intelligence experts in a multidisciplinary approach, is required to ensure the best outcomes for all. In addition, engagement of breast surgery patients in decisions where patients can be informed are important.

Economic considerations, job losses and the lack of human element pose additional ethical dilemmas. Machine learning may be stifled from practical implementation in breast surgery due to infrastructural shortcomings (with regards to both hardware and software) in the post-deployment management of models, a phenomenon that has been described within the technology's application within cardiology (43). Ethico-legal and social issues including the lack of regulatory structures surrounding the technology must be addressed and solutions to such issues within breast surgical care must be explored. Financial considerations and the accessibility of this technology in LMICs and globally, alongside the opportunity-cost of such applications, must also be considered. The technology should be widely accessible, and it is important to ensure the maintenance of high standards across different healthcare systems.

The most favourable studies included in this review included high sample sizes and were multicentre. Many of the single centre studies cited the idea of applying the relevant algorithm to larger sample sizes through involving data from other centres. Additionally, many studies circumnavigated the challenge of a low centre sample size by combinations with registry data to build their respective algorithms. Potential prospective solutions may also have basis in the concept of federated learning – a machine learning approach that allows an algorithm to combine data collectively from multiple centres without physical exchange of the data (46). Hence, it is clear that any future approaches should ensure that this collaborative approach is undertaken as standard. Many studies encountered additional issues with data imbalances such that some classes contained significantly larger amounts of data compared to others – to correct this, the Myung et al. study applied the ROSE:sMOTE oversampling technique which had been seen in previous literature (47) (34) and is a technique future studies may consider employing to increase the validity and generalisability of packages and consequentially the probability of success (21)(10).

Machine learning must be recognised as still within its trial phase – it is not perfect and subject to multiple flaws (26) (15). Although current literature provides fundamental foundations to its applicability, future approaches must consider clinical relevance at their core. The exact framework by which machine learning may seek to aid postoperative care must be established, as does the basis of a clinical decision support system. Such a system would aid the facilitation of greater data-based shared patient-clinician decision-making within breast surgical care. Hence, there is sufficient groundwork to construct prospective randomised studies to observe the impact of machine learning in clinical practice.

Significant and structured research is required to investigate the accuracy and utility of machine learning for the benefit of patients. It is important for surgeons to collaborate with computer scientists and related field specialists, so outcomes are directed towards improving patient care and to understand important limitations and ethical concerns relating to implementing such technology into everyday surgical practices.

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Figure legend:

Figure 1. PRISMA Flow Chart

Figure 2. Risk of bias diagram

Figure 3: Challenges and recommendation in Machine Learning research within Breast Surgery.

Table legends:

Table 1. studies included assessing the use of machine learning in breast surgery

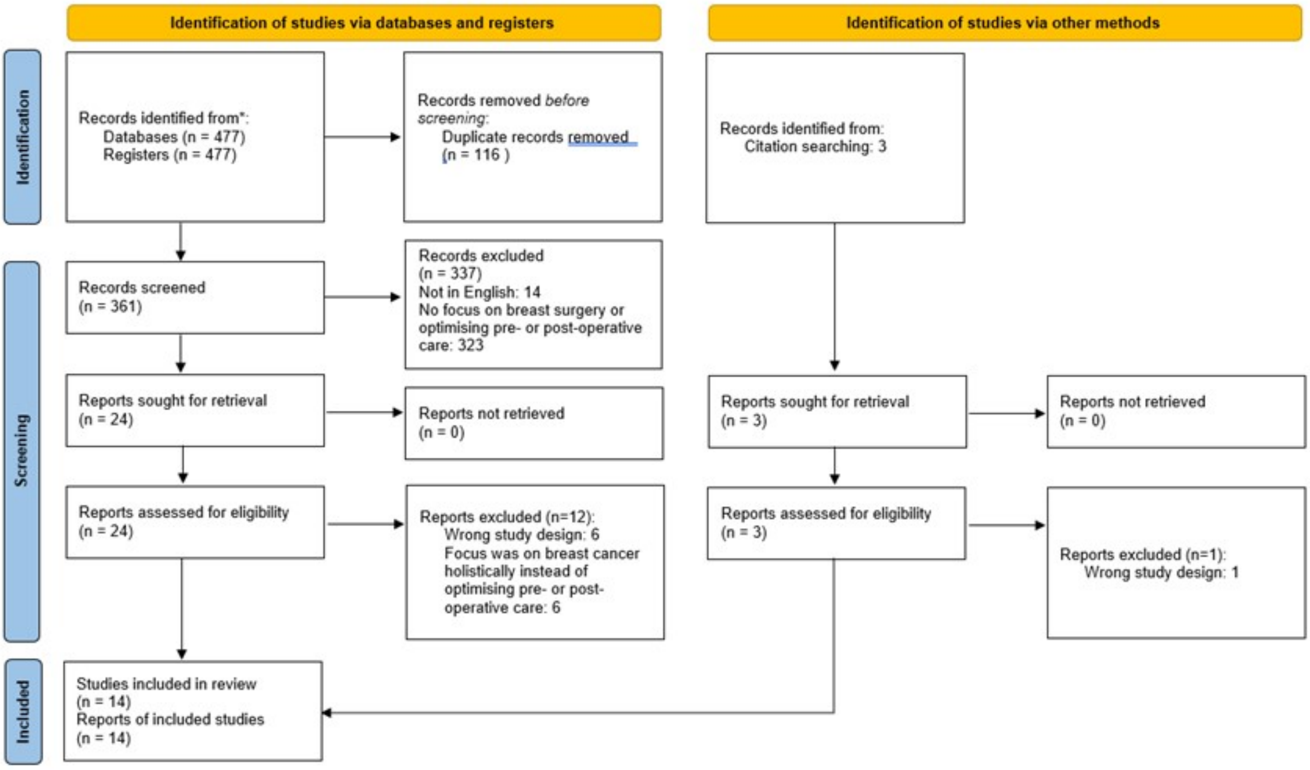
Table 1: studies included assessing the use of machine learning in breast surgery

Study	Year	Study design	Type of Procedure	Category of machine learning method utilised	Population Number	Method of machine learning implemented	Main reported outcomes
Becker et al	2017	NM, NR, NP	Mammography	Image analysis	3228	• Patients experiencing mammography at the institution were chosen to form the dataset - this was used to train the neural network. • An external dataset from the Breast Cancer Digital Repository was used for testing. This was appraised by three radiologists.	• One radiologist showed nearly equivalent performance to the network (0.83, p = 0.17) and the other two performed significantly better (0.91 and 0.94 respectively, p < 0.016). • The neural network's performance of 0.82 did not differ significantly between radiologist performance. The neural network behaved less specifically and more sensitively compared to humans throughout.
Dembrower et al	2020	M, NR, NP	Mammography	Screening	7364	• A cohort of mammograms were made selected in a way that mimicked frequency in reality. The AI cancer detector algorithm used had been pre-trained. • The software generates underlying image-level prediction scores for tumour presence. From this, cutoff points were established to insert patients into two novel work streams - on missed and additionally detected cancer.	• For 60%, 70% or 80% of women possessing the lowest AI scores in the negative radiologist stream, 0·3% (95% CI 0·0–4·3) / 2·6% (1·1–5·4) of screen-detected cancers would be missed respectively. For the 1% or 5% of women possessing highest AI scores in the 'enhanced assessment' stream, 12% or 27% of subsequent interval cancers, respectively, and 14% or 35% of next-round screen-detected cancers, respectively, may have also been able to be detected additionally.
Buda et al	2021	M, NR, NP	Digital breast tomosynthesis	Deep learning algorithm	16802	• 16802 digital breast tomosynthesis examinations that had 1 reconstruction view between August 26, 2014 and January 29, 2018 were analysed. • These were subdivided into 4 groups and further split into training and testing sets for the evaluation of the deep learning model.	• The deep learning model trained reached a breast-based sensitivity at 65% (39 of 60; 95% CI, 56%-74%) on the test set. This was at 2 false positives per DBT volume.
Huang et al	2017	M, NR, NP	Breast cancer surgery	Predictive model	3632	• This study compared three models (MLR, Cox & ANN) for 3632 post-operative breast cancer patients between 1996 and 2010. • An estimation dataset trained the model, and a validation dataset helped evaluate the performance of the model. Sensitivity analysis allowed the comparison of input variables for the model's predictions.	• The ANN model overall performed best over the MLR and Cox models for predicting 5-year breast cancer mortality post-operatively. • Age, Charlson comorbidity index (CCI), chemotherapy, radiotherapy, hormone therapy, breast cancer surgery volumes of hospital and breast cancer surgery volumes of surgeon were significant associations with 5 year breast cancer surgery, the latter was the most significant.
Juwara et al	2020	NM, NR, P	Breast cancer surgery	Predictive model	195	• 6 machine learning algorithms (least square, ridge, elastic net, random forest, gradient boosting and neural net) aided primary analysis of the identification of predictors of DN4-interview score (index for neuropathic pain). • Models were compared. A logistic classification model was created for neuropathic pain using the predictor outcomes of the primary analysis.	• Anxiety, type of surgery, preoperative baseline pain and acute pain on movement predicted DN4-score most pertinently. Anxiety had the most significant association with neuropathic pain. • The least square regression model compared well with the random forest model and neural network model. The Gradient boosting model performed better than all the other models.

Lotsch et al	2018	NM, NR, P	Breast cancer surgery	Supervised machine learning prediction	1000	• ML helped establish a short questionnaire to identify pain to the same predictive level as pre-existing full-form questionnaires. • The predictors were trained via the full set of items in Beck's Depression Inventory (BDI), Spielberger's State-Trait Anxiety Inventory (STAI), and the State-Trait Anger Expression Inventory (STAXI-2). • ML extracted features of these to create predictors with a lower item number.	• A 7-item set produced via ML that comprised 10% of the original questions from the STAI and BDI respectively performed the same as the full questionnaires in predicting development of persistent postsurgical pain.
Fu et al	2018	M, NR, NP	Breast cancer surgery	Detection	355	• A mobile health system allowed data to be collected based on real-time symptom reporting. • Both statistical and ML processes were employed for data analysis. Regarding the latter, 5 classical algorithms were compared: Decision Tree of C4.5, Decision Tree of C5.0, gradient boosting model (GBM), artificial neural network (ANN), and support vector machine (SVM).	• Using ML to compare different algorithms is a viable concept. Artificial neural network (ANN) performed best for detecting post-operative development of lymphedema (accuracy - 93.75%, sensitivity - 95.65% and specificity - 91.03%).
Lou et al	2020	M, NR, NP	Breast conservation surgery, modified reconstructive mastectomy, mastectomy with reconstruction	Predictive model	1140	• The cases in this study were divided into a training dataset to develop the ML model, a testing dataset for internal validation and an externally validating dataset. • After training, outputs of the model were taken for each training set. Accuracy in predicting breast cancer recurrence within 10 years was compared.	• The ANN model performed significantly best of all models based on sensitivity, specificity, PPV, NPV, accuracy, and AUROC values. • Surgeon volume followed by hospital volume and tumour grade were, in that order, best predictors of recurrence of breast cancer within 10 years.
Myung et al	2021	NM, NR, NP	Microsurgical unilateral breast reconstruction: muscle-sparing type TRAM and DIEP (muscle sparing type 3) abdominal flaps	Predictive model	568	• Neuralnet,, and RSNNS machine learning packages were applied to compare prediction accuracy, sensitivity, specificity, and predictive power (AUC) for predicting factors that raise abdominal flap donor site complications (against logistic regression). • 13 variables suggested to influence donor site complication rates were evaluated.	• Neuralnet performed most optimally of all the packages. • Fascial defect, history of diabetes, muscle sparing type, and presence or absence of adjuvant chemotherapy all significantly affected complication rate of donor sites. • High-risk group complication rates were significant compared to the low-risk group upon statistical analysis.
Van Egdom et al	2020	NM, NR, NP	Breast cancer surgery	Predictive model	764	• Various patient data variables were available. • ML methods (general linear model regression (GLM), support vector machines (SVM), single-layer artificial neural networks (ANN), and deep learning (DL)) evaluated presurgical prognostic factors of age, medical status, tumour characteristics, and (neo)adjuvant treatment indications or treatment characteristics.	• No relationship was determined between predictors and outcomes, rendering the model akin to the outcomes' respective population prevalence. Combining variables and, simultaneously, reducing dimensions, did not yield significant changes.
Yang et al	2021	NM, NR, NP	Breast cancer surgery	Predictive model	1061	• This study posed a predictive model of breast cancer recurrence based on clinical, nominal and numeric features. • 6 features from an initial dataset were identified for further processing and resampling. • AdaBoost and cost-sensitive learning packages predicted the	• AdaBoost reaches an accuracy of 0.973 and sensitivity of 0.675. A combination of AdaBoost and cost-sensitive learning poses a model with a reasonable accuracy of 0.468 and very high sensitivity of 0.947. Hence, the model is can be used to support early intervention.

						risk of recurrence and evaluated performance.	
Yap et al	2020	M, NR, NP	Breast ultrasound detection	Image analysis	469	• The study employs a deep learning method for breast ultrasound ROI detection and lesion localisation. Transfer learning is used to due to unavailability of datasets and a novel 3-channel artificial RGB method is applied for performance improvement. • This proposed method is evaluated and compared using an individual and composite dataset.	• Faster-RCNN outperformed a computer vision object detection algorithm indicating viability for use in BUS lesion localisation. • IoU (equivalent to Dice Coefficient Index) should be used in lesion detection due to its reliability.
Moncada-Torres et al	2021	M, NR, P	Breast-conserving surgery, mastectomy	Predictive model	36658	• Data of patients who underwent curative breast surgery was used to compare the performance of Cox proportional hazards analysis (CPH) with ML modes (Random Survival Forests, Survival Support Vector Machines and Extreme Gradient Boosting [XGB]) for survival predictions.	• ML models perform to at least the same standard as classical CPH regression and even better for some models (XGB). Furthermore, Shapley Additive Explanation (SHAP) values were used successfully as a form of explainable machine learning to provide detail on how the models' predictions are made.
Sidey-Gibbons et al	2021	NM, NR, P	Breast cancer surgery	Predictive model	611	• A set of oML algorithms (neural network, regularized linear model, support vector machines, and a classification tree) were trained and tested for making predictions of financial toxicity in a dataset. • The data were split into samples for the training and testing sets, prior to assessment of predictive performance.	• ML packages accurately predicted financial toxicity in this context demonstrating an AUROC of 0.85, accuracy of 0.82, sensitivity of 0.85, and specificity of 0.81. • Neoadjuvant therapy and autologous reconstruction were ascertained as key indicators of financial toxicity. • Radiation and tumour grade showed no effect.

M: multicentre; NM: non-multicentre; R: randomized; NR: non-randomized; P: prospective, NP: non-prospective


Identification of studies via databases and registers
Identification of studies via other methods
Identification
Records identified from*:
Databases (n = 477)
Registers (n = 477)
Records removed before screening:
Duplicate records removed
(n = 116)
Records identified from:
Citation searching: 3
Screening
Records screened
(n = 361)
Records excluded
(n = 337)
Not in English: 14
No focus on breast surgery or optimising pre- or post-operative care: 323
Reports sought for retrieval
(n = 24)
Reports not retrieved
(n = 0)
Reports sought for retrieval
(n = 3)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 24)
Reports excluded (n=12):
Wrong study design: 6
Focus was on breast cancer holistically instead of optimising pre- or post-operative care: 6
Reports assessed for eligibility
(n = 3)
Reports excluded (n=1):
Wrong study design: 1
Included
Studies included in review
(n = 14)
Reports of included studies
(n = 14)

Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Becker et al	+	+	+	+	-	-
Dembrower et al	+	+	+	+	+	+
Buda et al	-	+	+	+	+	-
Huang et al	+	+	+	+	+	+
Juwara et al	+	+	+	+	-	-
Lotsch et al	+	+	+	+	-	-
Fu et al	-	+	+	+	+	-
Lou et al	+	+	+	+	+	+
Myung et al.	+	+	+	+	+	+
Van Egdom et al	-	+	-	-	-	X
Xu et al	-	+	+	-	-	X
Yang et al	+	+	+	+	+	+
Yap et al	-	+	+	+	+	-
Gu et al	X	-	+	-	+	X
Bouaud et al	+	+	+	+	-	-
Moncada-Torres et al	+	+	+	+	-	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

Recommendations for the Adoption of Machine Learning in Breast Surgery

Challenge: Obtaining large-scale evidence

- Currently many case studies and proof of concept descriptions
- To overcome sample bias and improve representation for the best evidence
- Use **cohort studies** and large **randomised control trials**

Challenge: Inviting stakeholders

- Recognise the value of involving all stakeholders in design of ML processes
- Use **focus groups** and **expert interviews** when designing study protocols
- Improve synergy between ML and surgeons and promote understanding and leverage expertise

Challenge: Utilising the best dataset

- ML should mirror the target population as best as possible.
- Utilise **readily available data** or **combining existing datasets** in resource-poor settings.
- Use **transformation techniques** such as **oversampling** to reduce data imbalances