The Effect of Postoperative complications on Survival and Recurrence after Surgery for Breast Cancer: A Systematic Review and Meta-analysis

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Acknowledgements : Not applicable

Funding: The authors state that this work has not received any funding.

Conflict of Interest: The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article

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ABSTRACT

Background: This systematic review investigated the impact of complications on long term outcomes for patients with primary invasive operable breast cancer.

Methods: A systematic review was performed using appropriate keywords, and meta-analysis using a random effects model completed.

Results: Ten retrospective cohort studies, including 37657 patients were included. Five studies identified a relationship between wound complications, infection and pyrexia and recurrence or recurrence-free survival. Risk of recurrence, 1-year and 5-year recurrence-free survival and overall survival were related to complications, particularly for patients with poor Nottingham Prognostic Index. Five studies failed to demonstrate a relationship between complications and prognosis. Complication was found to significantly affect 5-year recurrence-free survival (HR 1.48 95% CI 1.02-2.14, p=0.04) but not recurrence (HR 2.39, 95%CI 0.94-6.07, p=0.07), with a high degree of heterogeneity among analysed studies (I2=95%).

Discussion: Further research is needed to quantify the effects of postoperative complication on prognosis following surgery for breast cancer.

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1. Introduction

Breast cancer is the most common cancer in the UK and accounts for 15% of all cancer cases[1]. Surgical therapy has long been the primary curative treatment for breast cancer, supported by advances in resection techniques and adjuvant therapies. However, ongoing deaths due to recurrence have raised a need for deeper understanding of the factors relating to metastasis and disease spread.

In 2008, Demicheli et al. reviewed the effects of surgery on tumour growth, suggesting that surgery played a role in tumour homeostasis, dormancy and surgery-driven enhancement of metastasis development[2]. This finding has its roots in work published more than a century earlier by Ehrlich and Apolant suggesting that competition for host-factors by synchronous tumours played a part in explaining tumour behaviour, and paved the way for our understanding of how surgery may interfere with this homeostatic process, in fact accelerating

disease progression[3]. Further work suggested that surgery may provide an escape from dormancy for micro metastases[4]. *In vivo* mouse models have supported this theory, proposing that we need to further assess the role of tumour-host interaction in disease dormancy and progression as these may prove to be targets for therapy [5-7]. Tumour and host-derived inflammatory pathways may offer prognostic information in breast cancer and elucidate mechanisms of metastatic spread [8]. However, it is clear that factors related to wound healing after surgery, particularly as they utilise similar pathways of angiogenesis and control of infection, may provide evidence of the role of postoperative inflammation in the natural history of cancer[9].

Dvorak described cancer as “wounds that do not heal”, suggesting that an overlap between carcinogenesis, maintenance of disease, and disease progression comparable to wound healing and surgical stress must exist[10]. Initially at the mercy of the host’s immune system, cancer may eventually reverse the effects of immunity to fuel its progress and incite metastasis through chronic and subsequently aberrant inflammation[11]. When observing the immunological landscape surrounding cancer’s natural history, cytokines such as TNF-alpha, IL6, PDGF and VEGF have all been implicated as tumorigenic and tumour promoting agents[10]. On a cellular level, the current understanding is that within T helper communities, T-Helper Type 1 (Th1) adaptive immunity plays a role in carcinogenesis, while Th-2 immunity may have a greater role in tumour progression[11-13].

Postoperative complications, described as “deviation from the normal postoperative course” can be classified in terms of severity or infective / non-infective aetiology[14]. Significant evidence of the effect of surgical complications has been described for colorectal cancer, and evidence now exists for the role of postoperative complications in determining outcomes for head and neck cancer, oesophageal and gastric cancer and lung cancer[15-25]. This has been purported to tie in with the role of pro-inflammatory pathways in determining the long term outcomes for cancer, including prostate and colorectal disease, where C-reactive protein (CRP), Ki67and Interleukin-6 (IL-6) have been implicated[26-28].

For breast cancer, initial evidence suggests that there may be a link between postoperative complication and recurrence risk[29-32]. In 2018, Beecher et al. suggested that wound complications affected outcomes for breast cancer patients, and single-centre retrospective evidence exists to support this [33, 34]. However, there are still a number of published reports suggesting that postoperative complications do not always negatively affect prognosis, leading to the need for objective comparison of the evidence [35, 36].

This review seeks to identify, evaluate and compare the current evidence for patients with primary invasive operable breast cancer who suffer postoperative complications, and establish whether these affect prognosis and survival.

2. Methods

2.1 Search Strategy

A study protocol was developed based on the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA-P) statement following a preliminary literature search in which key terms were piloted for inclusivity[37]. Search terms were focussed to reduce the return of irrelevant abstracts. An online literature search using EMBASE, PubMed and the Cochrane Library was performed in December 2019 to January 2020 to assess the role of postoperative complication on breast cancer prognosis. The final search terms were as follows:

- Breast Neoplasm, Breast Surgery, Mammaplasty (*OR)

AND

- Postoperative complication, Fever, Necrosis, Infection, Inflammation (*OR)

AND

- Prognosis, Systemic recurrence, Treatment outcome, mortality, neoplasm metastasis, neoplasm recurrence, survival (*OR)

Study inclusion criteria were as follows: Prospective or retrospective cohort studies within a well-defined study population; Patients with primary operable breast cancer; and patients who suffered postoperative complications or in whom postoperative findings were assessed for their potential association with survival, prognosis or recurrence were included.

Papers which did not have full text available, non-English and non-Human studies were excluded. Studies dedicated to metastatic breast cancer at diagnosis or exclusively to carcinoma in situ were excluded.

Two authors (FS and LR) performed a review of all eligible manuscript titles. The process is summarised in Figure 1. The bibliographies of the included articles were hand-searched for additional eligible studies. Any discordance in opinion with regards to the final texts was discussed between the two authors prior to final decision regarding inclusion.

Eligible studies were evaluated using the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist to assess quality, and scores are included in Table 1[38].

2.2 Data extraction

Each eligible paper was examined, and data collected. This included year of publication, stage of disease, size and age of population, inclusion and exclusion criteria, the use of adjuvant therapy, as well as definition of complications and prognostic indicators. Prognostic measures such as disease-free survival, total, locoregional and systemic recurrence rates as well as risk factors for postoperative complications were collected for comparison.

2.3 Data analysis

Data analysis using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform Meta-analysis of recurrence and survival. Hazard ratios for each outcome, from each study were combined using a random effects model to account for heterogeneity of methodology and complication type and reporting. Heterogeneity was assessed using the I^2 test and two-tailed *p*-values <0.05 was considered statistically significant. Only studies that performed multivariate analysis were included. For the purpose of meta-analysis, univariate HRs were used to reduce bias related to variable choice within each study population.

3. Results

Literature search yielded 9899 manuscripts. After excluding animal studies, non-English manuscripts and duplicates, 9874 manuscript titles were screened for relevance. Forty-six studies were evaluated using full text for eligibility according to criteria, and a final 10 papers were included in the final review[33-36, 39-44]. A summary of these studies is shown in tables 1-6.

3.1 Included Study Characteristics

10 studies were included, for a total of 37657 patients[33-36, 39-44]. The largest study, by Pedersen et al. included 30711 patients, whilst the smallest, by Abdullah et al. included 107 patients[35, 36]. Study characteristics are summarised in Table 1. The data was collected using patients diagnosed from 1985 to 2017. Median follow up was cited in 8 studies, ranging from 18 months to 229.3 months[43, 44]. Beecher et al. only included patients who had a minimum of five years follow up, whereas Mousa et al. had a mean follow up of 40 months[33, 42]. All studies were retrospective cohort studies. Two studies were based on Nationwide Database enquiry [36, 39]. Murthy et al. (35) studied a cohort based on a single-surgeon practice, while the remaining seven studies were single-centre [33-35, 40-44].

3.2 Tumour Characteristics

Tumour characteristics from each study are summarised in Table 2. Six papers included Union for International Cancer Control / American Joint Committee on Cancer (UICC/AJCC) Stage I-III disease, two papers included Stage IV, while two included early stage disease (stage I-II), of which one excluded nodal disease[33-36, 39-44]. Two other studies described the distribution of the Nottingham Prognostic Index (NPI) [33, 34, 36]. For those studies including nodal disease, five studies classified patients with regards to nodal disease positivity, classified disease into nodal stage, or quantified this into a different nodal classification depending on number of nodes identified[33, 34, 36, 41, 44]. Four studies included ductal, lobular and mixed cancer subtypes, while six studies did not clarify the included histological subtypes of breast cancer under review [33-36, 39-44].

With regards to surgical approach, these are summarised in Table 3. Indelicato et al. included only patients who underwent Breast Conservation Surgery (BCS), while four studies examined patients receiving either BCS or Mastectomy, of which the study by Murthy et al. also compared immediate versus no reconstruction for mastectomy patients[34, 36, 39-41]. For the five studies assessing patients with mastectomy only, O'Brien et al. compared immediate versus no reconstruction, whilst the remaining studies only observed patients undergoing immediate reconstruction, of which Mousa et al. looked in particular at alloplastic reconstructions[33, 35, 42-44]. Population characteristics are summarised in Table 4.

Six studies included patients who underwent neoadjuvant chemotherapy while the remaining four studies did not clarify their inclusion or exclusion[33-36, 39, 41-44]. Therapeutic characteristics for each included study are described in Table 5.

Tumour size was described in four studies, two papers classified cancers between 2cm (more and less than), while the remaining two separated larger tumour size as greater than 5cm and 6cm[34, 36, 40, 41]. Hormone receptor status was described in six studies, while HER-2 status was only addressed in three studies, with two of these defining the proportion of cases with triple-negative breast cancer[33, 34, 36, 40, 41, 44].

3.3 Complications and Recurrence

Overall rates of complication varied greatly amongst studies, although this can be explained by varying definitions of complications, from 2.5% (in the context of a single measured complication, reoperation for postoperative bleeding), to 26% (in the context of a single measured postoperative fever in 7 days following surgery), to 45% complications up to 90 days postoperatively in results reported by Mousa et al.[36, 40, 42]. This last study remains an outlier, particularly when comparing this research to other similar complication measurements, for which overall complication rates remained lower, even when including similar complication types and similar postoperative time scales.

Complications studied ranged from single studies looking at reoperation for bleeding (n=1) or postoperative pyrexia (n=1), however the majority of the papers included more than one complication[33-36, 39-44]. The period in which these complications were recorded varied from 7 days postoperatively to before the completion of adjuvant therapy[34, 40]. The most commonly observed and recorded complications were infection (n=8 studies); haematoma (n=6); and skin necrosis (n=6)[33, 35, 39, 40, 42-44]. Each complication and their relationship to recurrence and survival is described below.

Five studies were able to identify a relationship between complication and recurrence[33, 34, 39-41]. The details of complication rates and recurrence and survival effects are detailed in Table 6. Murthy et al. described a rate of wound complications of 9% (7% of all operations) when measuring from surgery to completion of adjuvant chemotherapy or radiotherapy[34]. Overall recurrence was 2%, of which 37% took place in patients who were noted to have wound complications. On univariate (UVA) and multivariate analysis (MVA), wound complication remained an indicator of increased risk of recurrence (Hazard Ratio 2.52(95% C.I.1.69-3.77)[34]. Five-year systemic recurrence-free survival (RFS) was also found to be more likely in patients with wound complications, an effect exacerbated for patients with poorer NPI scores ($p<0.0001$)[34]. Beecher et al. reported rates of complication of 23.1%, with 19.2% of total patients being found to have infection in the 30 days following surgery[33]. On UVA and MVA, wound complication, and then infection both remained risk factors for recurrence (MVA HR 4.61(95%C.I.2.72-8.95) for complications, HR 6.15(95%C.I.3.66-12.04) for infection)[33]. Overall systemic RFS was 85.6% for this cohort, with 5-year systemic RFS being reduced to 64% for those with complications ($p<0.001$)[33], suggesting exacerbation of effect for patients with poorer NPI scores ($p=0.001$ for poor NPI, $p=0.063$ for moderate NPI)[33].

De Glas et al. did not assess recurrence but observed survival outcomes, suggesting that 1-year survival, overall and relative survival (median follow up 86.4months, 12-168months range) were worse in patents with complications, although the effect was lost on multivariate analysis when adjusted for frailty and comorbidity indicators, suggesting that these may bear more impact in a study population which only included those above the age of 65 years[39]. Yan et al. described postoperative temperature of >38 degrees Celsius in 26% of their cohort in the 7 days post-surgery, and suggested that relapse events were more common in the patients with pyrexia ($p=0.004$)[40]. Relapse-free survival at 5 years was 88% in patients with postoperative fever versus 93% in those without fever ($p=0.0027$), proposing that this may be a contributor or an indicator of relapse risk although this association was lost when adjusted for Hormone receptor and ERBB2 status[40]. Indelicato et al. described a rate of

postoperative infection in the 3 months following surgery to be 7.7% and reported an increased risk of true local recurrence in these patients on MVA (p=0.001) [41].

Five studies did not identify an effect of the assessed complications on recurrence[35, 36, 42-44]. The study by Pedersen et al. was not able to demonstrate an effect of reoperation for bleeding in the first 14 days postoperatively on recurrence (median follow up 84 months), but did not consider survival outcomes[36]. Loss of effect of complications may be more difficult to demonstrate in the population under study which only included patients over the age of 65 years such as that seen by De Glas et al.[39]. Abdullah et al. examined surgical site infection and was unable to suggest a link to neither recurrence nor survival, albeit for a short follow up (median 47 months, 3-111months range). Despite relatively high complication rates, Mousa et al. did not demonstrate any relation between complication and locoregional or systemic recurrence after a mean follow up of 40 months[42].

Meta-analysis of three studies, by Pedersen, Murthy and Beecher including 32005 patients in which they reported the impact of complication on recurrence (Figure 2), failed to show a significant effect of complication on risk of recurrence (HR 2.39, 95%CI 0.94, 6.07 p=0.07)[33, 34, 36]. A high degree of heterogeneity (I^2=95%) was noted.

Meta-analysis of two studies, by Murthy and Beecher including 1294 patients in which they reported the impact of complication on 5-year recurrence-free survival (Figure 3), with a high degree of heterogeneity (I^2=95%), suggests a significant effect of complication on 5-year recurrence-free survival (HR 1.48 95%CI 1.02-2.14)[33, 34].

Local infection / Systemic Infection / Persistent wound discharge

Infection varied in definition between the included studies. De Glas et al. defined this as infection requiring intravenous antibiotics[39], whilst Indelicato et al. included patients with any evidence of erythema, tenderness and warmth focal to the site of surgery, and Abdullah et al. defined this according to the Center for Disease Control (CDC) definition of breast infection[35, 41]. O'Brien et al defined infection as drainage of pus from the wound, spontaneously or after debridement, whilst the remaining studies did not specify their definition of infection[43]. Rates of infection varied between 4.5% to 19.2%[33, 43]. In the study with the highest rates of infection (Beecher et al.), these reportedly formed 83% of all complications, which were identified in 23.1% of the entire patient population[33]. In this same study, wound complication was found to increase risk of recurrence on univariate (p<0.001) and multivariate (p<0.001) analysis, as well as reducing 5-year recurrence free survival (p<0.001)[33].

In data reported by de Glas et al. the rate of systemic infection (classified alongside wound infection) was 0.7% within 30 days from surgery, and when amalgamated into complications

as a group was shown to reduce 5 year relative survival, 5-year overall survival and 1-year overall survival[39].

Haematoma & reoperation for bleeding

Haematoma formation rates varied between 2% and 4%, although haemorrhage, when identified as a complication, was low in most corresponding studies ranging from 0.7% and to 4.8%, in which case associated anaemia was identified in 1.1% of the total cohort[39, 42-44]. Three studies identified haematoma as a potential complication responsible for increased risk of recurrence, while two studies who assessed haematoma formation were unable to demonstrate this effect[33-35, 39, 42]. In the three studies where haematoma (amalgamated into complications as a group) was reported to affect recurrence risk, 5 year recurrence free survival was also found to be affected ($p<0.001$, $p<0.001$, $p=0.022$) in three studies, with Beecher et al. suggesting exacerbation of the effect in poor NPI patient groups compared to moderate NPI ($P=0.001$)[33]. The study by de Glas et al. described reduced overall survival and relative survival in patients with all complications, raising the suggestion from the authors about the role of comorbidities and indicators of frailty in their older population for being greater determinants of survival than recurrence *per se*[39].

Pedersen et al. exclusively assessed the effect of reoperation for bleeding within 14 days of surgery, and did not demonstrate an effect on recurrence risk (Hazard ratio 1.06, 0.89-1.26)[36]. Two other studies examined reoperation for bleeding and/or haematoma[43, 44]. O'Brien et al. reported that overall, having a complication increased the risk of locoregional recurrence, although this was true only on multivariate analysis and was lost when adjusted for mastectomy alone versus mastectomy with immediate breast reconstruction, suggesting that mastectomy only patients, who had higher rates of complication and a usually higher disease stage were more likely to recur ($P<0.05$)[43]. Valente et al. suggested that postoperative complication, although this significantly delayed commencement of adjuvant therapy ($p<0.001$), did not lead to increased risk of recurrence (median follow up 90.48 months)($p=0.65$)[44].

Skin Necrosis

Skin necrosis rates were reported in 5 studies, while two additional studies did not clarify whether necrosis could be classed as "other wound problems including wound healing" or a wound complication [33-35, 39, 42-44]. Skin necrosis rates reported varied from 2.7% to 10%[42, 43]. When amalgamated into complications this was found to affect recurrence rate by Beecher et al., affecting both recurrence ($p<0.001$) and overall 5-year systemic recurrence-free survival ($p<0.001$)[33]. In the remaining 4 studies which expressly classified skin necrosis

or flap necrosis as a complication, no direct effect was identified on recurrence or survival[35, 39, 42-44].

Implant removal / Implant related problem / Flap loss

Reconstructive surgery was applied in 5 studies, and three of these expressly assessed implant problems as part of their complications[33, 34, 42-44]. Rates of implant loss varied from 3% to 15%, and none of these studies reported a significant effect of complication on rates or recurrence or survival[42, 44]. However, despite this, no significance was identified between rates of complication and recurrence in the entire population after a mean follow up of 35 months[42]. Conversely, O'Brien et al. reported that mastectomy-only patients (when compared to those with immediate breast reconstruction) had higher rates of seroma, and had higher rate of locoregional recurrence ($p<0.05$), although the direct link between complication and recurrence risk was not observed[43].

Pyrexia

One study exclusively assessed the relationship between pyrexia and recurrence of breast cancer, with a single measure of >38 degrees Celsius in the first 7 days following surgery[40]. In this study, 26% of patients were found to have postoperative temperatures of 38 degrees Celsius or more, which was found to be more common in older patients ($p<0.001$), patients with ERBB2 (Her-2) positive status ($p=0.003$), hypertensive patients ($p=0.011$), and in patients undergoing mastectomy (versus breast conservation surgery)($p=0.003$). In this study, postoperative fever was reported to be associated with reduced 5-year relapse free survival ($p=0.0027$), although this association was lost when adjusted for hormone receptor and ERBB2 status[40].

Wound dehiscence

Wound dehiscence was specifically classed as a complication in four studies, although a fifth study considers wound complication as a general group of complications, without providing specific rates of wound break down[33, 34, 39, 42, 44]. Rates of wound dehiscence varied from 1.2% to 16%, with the highest rate being composed of wound dehiscence together with infection[39, 42]. Within these five studies, one suggested that complications led to a delay in commencement of adjuvant therapy, but without increased risk of recurrence[44]. Two studies reported an effect of complications on recurrence and 5-year survival, although one was related to all wound complications ($p<0.001$), and the other study suggested that in the presence of multiple comorbidities, the effect of complications on 5-year and 1-year overall survival and 5-year relative survival was lost, suggesting that frailty or comorbid conditions may have a more significant impact on survival in a population older than 65 years[33, 39].

Re-admission & need for revisional surgery

Two studies considered re-admission to be a form of postoperative complication and assessed their impact on recurrence ad survival[42, 44]. Valente et al. reported their rates of readmission (10.9%)[44]. However, neither study reported a significant effect of complication on recurrence or survival, despite reporting increased rates of complications in older patients, patients with previous chest wall radiation and complications leading to delayed commencement of adjuvant therapy[42, 44].

Seroma

Seroma was classified as a complication in three studies, with a fourth suggesting that persistent discharge from a wound was considered a complication[34, 42-44]. Within the three studies that clearly classified seroma as a complication, this was shown to affect recurrence and survival by De Glas et al. in the context of older patients who did not have comorbidities and by O'Brien et al. in patients who had mastectomy (versus mastectomy and immediate breast reconstruction), who tended to have significantly higher disease stage and specifically had higher seroma rates($p<0.05$)[39, 43].

Anaemia

De Glas et al. described anaemia as a complication, measuring 1.1% rates of anaemia in the <30 days following mastectomy and immediate breast reconstruction[39]. No assessment of recurrence was performed in this study, which only included patients over 65 years, but 1-year and 5-year overall survival ($p=0.025$, $p=0.022$) and 5-year relative survival ($p=0.002$) was worse in patients with complications although this effect was lost after including patients with comorbidities[39].

Delirium

De Glas et al. assessed the impact of delirium in the first 30 days after surgery, reporting rates of 0.3%[39]. One-year and 5-year overall survival and 5-year relative survival was worse in patients with complications as a whole, although this effect was lost after including patients with comorbidities[39].

Cardiovascular / Thromboembolic disease

Two papers included thromboembolic disease as a complication, with De Glas et al. additionally specifying cardiovascular complications such as arrhythmias[39, 43]. In the paper reporting these complications separately, thromboembolism was found in 0.1% patients, and cardiovascular complications in 0.7% patients within 30 days of surgery[39]. No assessment of recurrence was performed in this study, which only included patients over 65 years of age,

but 1-year and 5-year overall survival and 5-year survival was worse in patients with complications, although this effect was lost after including patients with comorbidities after a median follow up 86.4 months (range 0.12-168) [39]. The second study, by O'Brien et al. included deep vein thrombosis with other complications such as UTI, skin rash and phlebitis in the 90 days following surgery, and reported combined complication rates of 2.7%, stating that all complications were found to significantly increase time to adjuvant therapy but without an effect on recurrence after a median follow up of 229.3months (range 166-367)[43].

3.4 Potentially Confounding Factors

Five studies identified additional pre-operative factors which impact on complications, recurrence and survival within their cohort [33, 34, 41, 43, 44].

Valente et al. identified smoking to be associated with increased recurrence[44]. In this study, 14% of all patients were smokers, and although they were not more likely to develop complications, they did have a significantly higher chance of recurrence (p=0.043)[44].

Valente et al. also identified tumour stage (p=0.024), histology (p=0.023) nodal status (p=0.001), as well as UICC/AJCC stage (p=0.047) and tumour grade (p=0.036) to significantly impact on risk of recurrence, and that tumour histology was also related to risk of surgical complication (p=0.034)[44].

Beecher et al. reported that patients who underwent chemotherapy and radiotherapy had a significantly higher risk of recurrence (p=0.020, p=0.011, respectively), although this correlates with their finding that patients with lymphovascular invasion (p=0.002), poorer NPI (p<0.001), and positive nodal status (p<0.001) also had a higher risk of recurrence, together with complications in general (p<0.001), and infection in particular (p<0.001)[33]. This effect was maintained on multivariate analysis only for NPI status (p=0.003), wound complications (p<0.001) and infection (p<0.001), again suggesting that NPI status, which takes into account disease stage and affects clinical decision making with regards to treatment, may be more significantly indicative of risk of recurrence than the type of medical therapy which itself is influenced by tumour and patient factors[33].

Three studies identified type of surgery as a significant effector on recurrence[34, 43, 44]. One study reported that, allowing for a limited comparison between mastectomy and mastectomy with reconstruction patients (often younger and with more frequently non-invasive disease), mastectomy patients were more likely to develop seroma postoperatively, and were more likely to develop recurrence over a median follow up of 20 months (range 1-53)[43]. Murthy et al. reported that when comparing mastectomy to wide local excision, wherein 55.6% underwent mastectomy, this was associated with a higher risk of systemic recurrence on

univariate and multivariate analysis (p<0.0001, p=0.003, respectively), as well as risk of complication, itself an independent indicator of risk of systemic recurrence (p<0.0001)[34].

Yan and colleagues described that patients who were HR/ERBB2 negative had a higher risk of postoperative fever 7 days postoperatively (p=0.003), and on multivariate analysis were also shown to have lower recurrence-free survival (p=0.013), together with patients with fever (p=0.044)[40].

4. Discussion

This systematic review and meta-analysis suggest that postoperative complications, namely postoperative pyrexia, and infective wound complications appear to be related to effects on recurrence and survival outcomes in certain studies. However, an equal number of studies suggest lack of evidence on this topic. To date, no other review has been performed to assess the impact of complications on prognosis in primary operable breast cancer. Meta-analysis was limited by the relative heterogeneity of outcome data provided within the reviewed studies but prompts further study.

The significant heterogeneity in the study populations, follow-up timescale (often <10 years), surgical options available to patients, outcome measures and type of complication recorded significantly limits the current conclusions that can be made at present. Confounders such as smoking status, surgical technique and tumour prognostic scores suggest that the relationship between postoperative complications and prognosis is complex.

Tumour and host-derived inflammation has been identified as a marker of pre-operative prognosis, and an indicator of risk of metastatic disease[8]. However, it is clear that factors related to wound healing after surgery, particularly as they utilise similar pathways of angiogenesis and control of infection, may provide evidence of the role of postoperative inflammation in the natural history of cancer[9]. More recently, there has been a call for more research looking at the immediate postoperative period as a highly influential period in determining prognosis, out of proportion to its relative length compared to the pre-operative and longer term medical period for cancer patients[45]. Understanding how postoperative complications, and by extension, the immune landscape of cancer in the perioperative period affect clinical outcomes may reveal immunotherapeutic options for cancer patients[45].

In the era of “individualised therapy” options for patients with breast cancer which now encompasses breast conservation, oncoplastic and reconstructive surgery, and with increasing use of neoadjuvant and adjuvant systemic therapy, patients are subjected to varying levels of risk, and must be counselled individually when embarking upon their surgical therapy. Comorbidities, increasing age, disease stage and prognostic scores themselves can

be responsible for decisions regarding therapy, surgical technique, and expected survival outcomes, therefore a well-planned analysis of a broad but compartmentalised cohort is crucial.

Another challenge to our current understanding of the role of inflammation in breast cancer is the absence of objective measure of inflammatory indicators in the context of surgery and postoperative complications. Previous work by Watt et al. in colorectal cancer has identified how there is a predictable, measurable inflammatory response following surgery (through the measure of serum markers such as C-Reactive Protein, CRP), while accepting that the presence of confounders such as postoperative complications may influence this[46]. Within this systematic review, studies looked at reported outcomes in a retrospective fashion, and therefore prognostic measurements in future study would may reveal insights into whether it is the surgery itself, or the expected severity or prolongation of inflammation after complications which have a more significant impact on prognosis. Stratification of severity of complication, either using well-accepted scales such as Clavien-Dindo or objective serological indicators such as CRP or white cell subsets such as neutrophil count would be helpful in stratifying the rapport between inflammation and prognosis[14]. Together with this, the additional concern that surgical technique itself affects postoperative inflammation (as evidenced by a smaller inflammatory marker rise in laparoscopic versus open abdominal surgery for colorectal cancer) suggests that studying a population according to each surgical technique may allow greater granularity of results regarding prognosis after complication[46]. Different subsets of breast cancer, in itself a heterogeneous cancer group, may also have different effects on the local immune response, proposing that knowing the (objectively measured) inflammatory landscape of the patient before surgery may also help guide decisions about surgical intervention by indicating the expected clinical outcomes[45]. This in turn may explain how within this review, certain groups such as triple-negative receptor patients, or patients with higher comorbidity scores, had poorer outcomes, and particularly in the context of reoperation for bleeding or postoperative pyrexia, the latter itself a possible indicator of a “pro-inflammatory” state even before surgery.

The results of this review suggest that despite limitations posed by confounders and study design, further research is justified. Using a well-defined and stratified population according to risk, age and comorbidities, together with appropriate control of confounders and with appropriate length of follow up may reveal how postoperative complications impact on prognosis in breast cancer.

Funding: This research received no external funding.

Conflicts of interest: The authors declare no conflicts of interest.

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