Quality of life in patients with breast cancer with neoadjuvant chemotherapy: a systematic review

Yueqiu Zhao, Licong Chen, Xiaoqing Zheng, Yulan Shi

ABSTRACT

Objectives The aims of this systematic review were to assess the impact of neoadjuvant chemotherapy (NAC) on breast cancer (BC) patients’ quality of life (QOL), to compare the different regimens of NAC on BC patients’ QOL, to compare NAC versus adjuvant chemotherapy on BC patients’ QOL and to identify predictors of QOL on patients with BC receiving NAC.

Design The design used Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources Cinahl, Embase, PubMed, Scopus, Web of Science, Cochrane library and PsycINFO were searched through 27 December 2021.

Eligibility criteria for selecting studies The inclusion criteria were included: patients with BC receiving NAC, outcome measures related to QOL and published in English. The exclusion criteria were included: duplicates or overlapping participants, not original research, data or full text not available and qualitative study.

Data extraction and synthesis Two independent reviewers used standardised methods to search, screen and code included studies. The risk of bias in individual studies was evaluated with Cochrane collaboration’s tool for assessing risk bias, Newcastle Ottawa Score or Joanna Briggs Institute Critical Appraisal tool. This systematic review performs narrative synthesis based on several different themes.

Results The initial search resulted in 2994 studies; 12 of these studies fulfilled inclusion criteria. There was no significant difference in the QOL of BC before and after NAC, but patients experienced adverse reactions and depression during chemotherapy. Different regimens of NAC have different effects on patients’ QOL. Patients with NAC had more severe physical discomfort than those with adjuvant chemotherapy. However, BC patients’ QOL can be improved by intervening on social or family support, and these predictors, including chronotype, QOL before NAC and depression.

Conclusions More original research is needed in future to understand the profile and predictors of QOL in patients with BC on NAC, which will help clinicians and patients make decisions and deal with NAC-related issues.

INTRODUCTION

Breast cancer (BC) is the most common disease in women worldwide, with the prevalence now surpassing lung cancer as the leading global cancer incidence in women in 2020, with 11.7% of all new cases (2.3 million); and it is the fifth leading cause of cancer deaths worldwide, accounting for 6.9%.1 Treatment of BC usually consists of two parts: local surgical treatment and systemic treatment; systemic treatment can precede surgical treatment (neoadjuvant) or follow it (adjuvant).2 Neoadjuvant chemotherapy (NAC) is used in patients with locally advanced BC or inoperable BC to improve the likelihood of breast-conserving surgery by reducing the size of the tumour in the past. Current studies have shown that NAC can also be used in the treatment of patients with early-stage operable BC to improve cosmetic outcomes and reduce postoperative complications, such as lymphoedema and prolong survival.3,5 NAC is associated with improved survival compared with adjuvant chemotherapy in patients with triple-negative BC only after complete pathologic response,6 and the same effect has been observed in other cancers like bladder cancer and colon cancer.7,8 NAC is widely used, while more and more scholars are studying the survival outcomes of patients after NAC, such as pathologic complete response, disease-free survival and overall survival.4,9 However, the goals of cancer treatment should include not only survival outcomes but also quality of life (QOL), which is an important outcome measure in clinical investigations and survival studies in BC.10–12 Now, the treatment regimens of BC are numerous and effective, but the side effects associated with different treatment modalities and the impact on QOL are different. So, optimal
stratification and ranking of treatment strategies should focus on individual risk profiles as well as QOL. Meanwhile, QOL is a major factor in treatment decisions for advanced or metastatic disease. It is worthwhile to consider the choice of an effective, least toxic anticancer treatment before implementing definitive therapy. Therefore, studying the QOL of NAC patients and comparing it to other treatments can help patients and clinicians make decisions.

The aims of this systematic review were (1) to assess the impact of NAC on BC patients’ QOL, (2) to compare the different regimens of NAC on BC patients’ QOL, (3) to compare NAC vs adjuvant chemotherapy on BC patients’ QOL and (4) to identify predictors of QOL on patients with BC receiving NAC.

METHODS
We primarily followed the Joanna Briggs Institute guidelines on systematic reviews and we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (figure 1).

**Search strategy**
A systematic search of the following databases was performed: CINAHL, Embase, Pubmed, Scopus, Web of Science, Cochrane library and PsycINFO. The final search was in December 2021. Three categories of terms were searched: (1) BC, (2) NAC and (3) QOL. In PubMed and Cochrane library, medical subject headings were used (breast neoplasms, neoadjuvant therapy, QOL, sexuality, anxiety, depression and social support). In Embase, Emtree terms were exploded (breast tumour, NAC, QOL, sexuality, anxiety, depression and social support). In Scopus, Web of Science, CINAHL and PsycINFO, only keywords were used (online supplemental material 1).

**Data analysis**
The inclusion criteria were as follows: (1) adult patients (18 years older); (2) patients with BC receiving NAC; (3) outcome measures related to QOL, including QOL, psychological impact, support from various sources and so on and (4) published in the English language. The exclusion criteria were as follows: (1) data could not be extracted; (2) duplicates or overlapping participants; (3) not original research, such as commentaries, editorials or reviews; (4) full text not available and (5) qualitative study. Two independent researchers (YZ and XZ) screened for potentially relevant studies by reviewing abstracts. The full texts were then screened further according to the inclusion and exclusion criteria. Any uncertainty was solved by a third researcher (YS). Two researchers (YZ and XZ) independently extracted and recorded the following information from the enrolled studies: author, published year, country, study design, sample size, age, regimens of NAC, timing of assessment, instrument and outcomes. The risk of bias in individual studies was evaluated by two independent researchers (YZ and LC) in accordance with Cochrane collaboration’s tool for assessing risk bias, or Newcastle Ottawa Score (NOS) or Joanna Briggs Institute Critical
Appraisal tool. Any disagreement was resolved by a third researcher (YS).

**Patient and public involvement**

Patients or the public were not involved in the conceptualisation or carrying out of this research.

**RESULTS**

**Flow of included studies**

An initial search identified a total of 2994 studies (PubMed: 98, Scopus: 1191, Embase: 281, Web of Science: 1011, CINAHL: 89, Cochrane library: 35 and PsycINFO: 189). After removing the duplicates, the total number of studies left was 2527 and all of these were screened. On screening, 2223 studies failed to meet our inclusion criteria and were removed from the analysis. The full text was obtained for 104 studies. Out of these 104 studies, an additional 92 were excluded and 12 met our inclusion criteria as defined above (figure 1).

**Risk of bias in the included studies**

The quality of cohort studies was assessed by NOS, randomised controlled trials (RCTs) by Cochrane collaboration’s tool and cross-sectional study by Joanna Briggs Institute Critical Appraisal tool (online supplemental tables S1–S3).

**Characteristics of included studies**

Seven studies were designed as prospective cohort studies,20–25 three were RCTs,26–28 one was a retrospective cohort study,29 and one was a cross-sectional study.30 Two studies were each from Brazil25 27 and Korea,21 31 and one each from China,20 Japan,29 India,22 UK,26 Germany,23 Indonesia,26 Iran24 and the USA.28 One study compared QOL in BC patients with NAC and adjuvant therapy,26 and three studies compared QOL in patients with different regimens of NAC. Chel-lapan22 showed that there was no difference in physical problems between the weekly regimen of paclitaxel and the 3-weekly regimen of paclitaxel. Rezapour et al24 reported that QOL declined in both doxorubicin and cyclophosphamide (AC) and paclitaxel and gemcitabine (PG) groups, but the two were reflected in different symptoms. The AC group had a significantly better situation in fatigue, pain, cognitive functioning and constipation compared with the PG group. Nausea and vomiting, dyspnoea, insomnia and diarrhoea were better in the PG group. There was no statistically significant difference in physical performance and physical capability between the two groups. Walker et al26 reported patients had severe pain in the 3-weekly group compared with the weekly docetaxel group (p=0.034).

**Neoadjuvant versus adjuvant chemotherapy**

Only one study compared the effects of neoadjuvant and adjuvant chemotherapy on physical symptoms. Coelho et al27 observed that QOL was altered with the greater loss for getting NAC compared with adjuvant. Physical function and dyspnoea symptoms had a greater impact in the neoadjuvant group compared with the adjuvant group. It is attributed to late diagnoses that provide aggressive treatments.

**Intervention in NAC**

Two of these studies intervened in BC patients on NAC. Souza et al27 showed that nutritional interventions improved patients’ grip strength, positively affected the occurrence of nausea/vomiting and loss of appetite, and reduced the frequency of leucopenia and abdominal pain during NAC. Basen-Engquist et al28 reported that...
<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size (n)</th>
<th>Age</th>
<th>Regimens of NAC</th>
<th>Timing of assessment</th>
<th>QOL-related instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding et al.20</td>
<td>2019</td>
<td>China</td>
<td>Prospective cohort study</td>
<td>29</td>
<td>46±8</td>
<td>CEF regimen</td>
<td>Before and after NAC</td>
<td>EORTC QLQ-C30</td>
</tr>
<tr>
<td>Lee et al.21</td>
<td>2017</td>
<td>Korea</td>
<td>Prospective cohort study</td>
<td>134</td>
<td>44.48±7.48</td>
<td>Anthracycline-based regimens along with standard doses of antiemetics</td>
<td>Before and after the first cycle of NAC</td>
<td>PSQI, HADS, MAT</td>
</tr>
<tr>
<td>Takada et al.29</td>
<td>2018</td>
<td>Japan</td>
<td>Retrospective cohort study</td>
<td>300</td>
<td>55 (27–90)</td>
<td>FEC-paclitaxel (HER2-positive + trastuzumab)</td>
<td>Before and after NAC</td>
<td>QOL-ACD-B</td>
</tr>
<tr>
<td>Chellappan et al.22</td>
<td>2018</td>
<td>India</td>
<td>Prospective cohort study</td>
<td>50 (weekly) vs 50 (3-weekly)</td>
<td>–</td>
<td>0 patients: paclitaxel and doxorubicin (4 course) every 3 weekly</td>
<td>Weekly (total 10 weeks)</td>
<td>HAM-D, FACT-B, FACT-Taxane</td>
</tr>
<tr>
<td>Walker et al.26</td>
<td>2011</td>
<td>UK</td>
<td>RCT</td>
<td>41 (weekly) vs 41 (3-weekly)</td>
<td>–</td>
<td>Weekly: AC+weekly docetaxel 3-weekly: AC+3-weekly docetaxel</td>
<td>Before randomisation, every 3 weeks during docetaxel, and 3 weeks after completion of chemotherapy</td>
<td>FACT-B, RSCL, HADS, MRS, GDS, TSEQ</td>
</tr>
<tr>
<td>Hermelink et al.23</td>
<td>2007</td>
<td>Germany</td>
<td>Prospective cohort study</td>
<td>101</td>
<td>48.6±9.7</td>
<td>Standard chemotherapy or dose-intensified therapy</td>
<td>Before and toward the end of NAC</td>
<td>FEDA, Cognitive Function Scale of EORTC QLQ-C30; HADS</td>
</tr>
<tr>
<td>Aprilianto et al.30</td>
<td>2021</td>
<td>Indonesia</td>
<td>Cross-sectional study</td>
<td>56</td>
<td>–</td>
<td>Almost half (33.9%) of respondents were between the ages of 41–50 years old.</td>
<td>–</td>
<td>A self-made family social support questionnaire, RSES</td>
</tr>
<tr>
<td>Rezapour et al.24</td>
<td>2018</td>
<td>Iran</td>
<td>Prospective cohort study</td>
<td>50 vs 50</td>
<td>28–70</td>
<td>AC vs PG regimens</td>
<td>At the beginning and end of chemotherapy</td>
<td>EORTC QLQ-C30</td>
</tr>
<tr>
<td>Coelho et al.25</td>
<td>2017</td>
<td>Brazil</td>
<td>Prospective cohort study</td>
<td>53 (NAC) vs 14 (adjuvant chemotherapy)</td>
<td>51.3 (30–77)</td>
<td>NAC: anthracyclines and taxanes Adjuvant chemotherapy</td>
<td>–</td>
<td>EORTC QLQ-C30, QLC-BR23</td>
</tr>
<tr>
<td>Souza et al.27</td>
<td>2021</td>
<td>Brazil</td>
<td>RCT</td>
<td>19 (IG) vs 15 (CG)</td>
<td>44.3±9.2 (IG) vs 45.5±8.6 (CG)</td>
<td>AC regimen</td>
<td>T0: before the beginning of the first cycle T1: during the second cycles T2: during the third cycles T3: until the end of the third one</td>
<td>EORTC QLQ-C30, HGS</td>
</tr>
<tr>
<td>Basen-Engquist et al.28</td>
<td>2020</td>
<td>USA</td>
<td>RCT</td>
<td>19 (IG) vs 18 (CG)</td>
<td>49.6±13.3 (IG) vs 49.2±9.2 (CG)</td>
<td>–</td>
<td>T0: at baseline T1: mid-chemotherapy (3 months) T2: post-chemotherapy (6 months)</td>
<td>SF-36, BIS</td>
</tr>
<tr>
<td>Lee et al.31</td>
<td>2021</td>
<td>Korea</td>
<td>Prospective cohort study</td>
<td>193</td>
<td>44.8±7.913</td>
<td>Four sessions of anthracycline and cyclophosphamide, followed by 4 sessions of docetaxel</td>
<td>T0: before the first session of NAC T1: before the start of the last session of chemotherapy T2: 6 months after the end of chemotherapy</td>
<td>HADS, FACT-B</td>
</tr>
</tbody>
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*AC, doxorubicin and cyclophosphamide; BFI, Brief Fatigue Inventory; BIS, Body Image Scale; CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; CES-D, Center for Epidemiologic Studies-Depression Scale; CG, control group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-Taxane, Functional Assessment of Cancer Therapy-Taxane; FEC, fluorouracil injection, epirubicin, and cyclophosphamide; FEDA, Fragebogen erlebter Defizite der Aufmerksamkeit (Questionnaire of Experienced Attention Deficits); GDS, Global Distress Scale; HADS, the Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; HGS, handgrip strength; IG, intervention group; MAT, Multinational Association of Supportive Care in Cancer Antiemesis Tool; MRS, Mood Rating Scale; NAC, neoadjuvant chemotherapy; NAST, neoadjuvant systemic therapy; PG, paclitaxel and gemcitabine; PSQI, Pittsburg Sleep Quality Index; QLQ-BR23, the Quality of Life Questionnaire-Breast Cancer Module; QOL-ACD-B, Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs-Breast; RCT, randomised controlled trial; RSCL, Rotterdam Symptom Checklist; RSES, Rosenberg Self Esteem Scale; SF-36, 36-Item Short Form Health Survey Questionnaire; TSEQ, Treatment Side-Effects Questionnaire.*
| Subjects         | Themes                 | Study (n) | Author                           | Outcomes                                                                                                                                 |
|------------------|------------------------|-----------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Physical symptoms| Body image 1           | Basen-Engquist et al. 28 | The difference in body image was not significant between IG and CG.                                                                      |                                                                                                                                                                                                 |
|                  | Nausea/vomit 2         | Lee et al. 21          | 48.5% of patients undergoing NAC experienced CINV.                                                                                      | Nutritional interventions during NAC positively affected the occurrence of nausea/vomiting and loss of appetite.                                                                               |
|                  | Fatigue 2              | Ding et al. 20         | Patients experienced increased fatigue after NAC.                                                                                       | The PG group had increased fatigue than the AC group.                                                                                                                                       |
|                  | Cognitive function 2   | Rezapour et al. 24     | During NAC, cognitive function remained stable in most patients, but cognitive decline predominated in 27% of patients.                  | The PG group had impaired cognitive function than the AC group.                                                                                                                              |
|                  | Dyspnoea 3             | Ding et al. 23         | Patients experienced increased dyspnoea after NAC.                                                                                       | The AC group had increased dyspnoea than the PG group.                                                                                                                                         |
|                  | Pain 3                 | Takada et al. 29       | Before NAC, the low QOL group had significantly lower scores on the subscale of Physical symptoms and pain than the high QOL groups(p<0.001). However, there was no significant difference between the two groups after NAC. | Nutritional interventions reduced the frequency of abdominal pain during NAC.                                                                                                                   |
|                  | Other symptoms 5       | Chellappan et al. 22   | There was no difference in physical problems between the weekly regimen of paclitaxel and the 3-weekly regimen of paclitaxel.            | The AC group had a better role function compared with the PG group.                                                                                                                             |
|                  | Anxiety/depression 3   | Lee S et al. 21        | Before NAC, the low QOL group had significantly lower scores on the subscale of Dress, sexual aspect, other categories than the high QOL groups(p<0.001). However, there was no significant difference between the two groups after NAC. | The depression in BC patients was most severe during NAC compared with before and after NAC. Anxiety was most severe before NAC but gradually improved throughout the treatment session. |
|                  |                       | Lee KM et al. 21       | 40 patients were anxious and 49 were depressed. In the univariate analyses, overall CINV was significantly associated with anxiety (p=0.038). | Nutritional interventions improved patients’ grip strength, positively affected the loss of appetite and reduced the frequency of leucopenia during NAC. |
|                  | Emotional function 4   | Chellappan et al. 22   | Three weekly patients had more problems regarding emotional well-being than weekly patients. But the observed difference in scores of depression among the two groups was not statistically significant. | The AC group had better emotional functioning compared with the AC group.                                                                                                                         |
|                  | Social function 4      | Chellappan et al. 22   | Weekly group had a high level of social well-being than 3-weekly group.                                                                 | Differences in role emotional were not significant between IG and CG.                                                                                                                           |
| Support          | Family support 1       | Aprillianto et al. 30  | 36 respondents (64.3%) were in a good category of family social support. The self-esteem of almost half of the BC patients (27 respondents or 48.2%) was in a moderate level category. |                                                                                                                                                                                                 |
|                  | Social function 4      | Chellappan et al. 22   | Weekly group had a high level of social well-being than 3-weekly group.                                                                 | Differences in social function of IG and CG groups were not significant.                                                                                                                        |
|                  |                       | Walker et al. 26       | There was no significant difference in the social dimension between weekly group and 3-weekly group.                                                                                           | The AC group had better social function compared with the PG group.                                                                                                                             |

AC, doxorubicin and cyclophosphamide; BC, breast cancer; CG, control group; CINV, chemotherapy-induced nausea and vomiting; IG, intervention group; NAC, neoadjuvant chemotherapy; PG, paclitaxel and gemcitabine; QOL, quality of life.
weight gain prevention intervention reduced more in waist circumference (p=0.03) and greater improvements in self-reported vitality scores (p=0.03) compared with the control group. The majority of participants reported being satisfied with the intervention during chemotherapy (88%).

Psychological effects
Eight studies evaluated psychological effects during NAC and 52% of patients get negative effects on psychological aspects (table 2; figure 2). Four studies evaluated emotional function,22 24 25 28 three studies evaluated anxiety/depression21 26 31 and two evaluated role function.24 27 Lee et al21 reported that the depression in BC patients was most severe during NAC compared with before and after NAC. Anxiety was most severe before NAC but gradually improved throughout the treatment session. Lee et al21 reported that overall CINV was significantly associated with anxiety.

Different regimens of NAC
Three studies investigated the changes in psychological effects with different regimens of NAC. Chellappan et al22 studied NAC with different regimens and showed that patients who were treated once a week had a high level of emotional well-being than those who were treated three times a week. But depression among the two groups was not statistically significant. Meanwhile, Walker et al20 found anxiety and depression were not statistically different between the weekly group and the 3-weekly group. Rezapour et al24 reported that the AC group had a high level of role functioning than the PG group. The emotional functioning was better in the PG group compared with the AC group.

Neoadjuvant vs adjuvant chemotherapy
One study investigated the psychological effects between NAC and adjuvant chemotherapy. Coelho et al25 reported that emotional function was significantly affected in adjuvant chemotherapy and NAC, but there was no difference in the effects of the two treatments.

Intervention in NAC
Two studies intervened in BC patients on NAC. Souza et al26 reported that nutritional interventions were able to improve the role function. Basen-Engquist et al28 reported that weight gain prevention intervention did not change mental health or role emotion.

Support
Five studies evaluated support from society or family and 55% of patients did not receive adequate support (table 2; figure 2). Aprilianto et al29 reported that 64.3% of the respondents reported that social support for the patient's family was mostly in the good category, and 48.2% of the patients with BC had a moderate level of self-esteem. There was a strong positive correlation between family social support and patient self-esteem.

Different regimens of NAC
Three studies evaluated support between different regimens of NAC. Chellappan et al22 reported that weekly group had a high level of social well-being than 3-weekly group (p=0.007). Rezapour et al24 reported that the AC group had significantly better social function compared with the PG group. Walker et al20 showed that the weekly group and the 3-weekly group had no significant difference in the social dimension.

Intervention in NAC
Basen-Engquist et al28 reported that weight gain prevention intervention couldn’t change social function of patients.

QOL-related predictors
Three studies have extrapolated QOL-related predictors of BC patients during NAC: chronotype, QOL before NAC, and depression.21 29 31 Lee KM et al31 suggest late chronotype may be a predictor of CINV. Patients with BC with late chronotype have an increased risk of CINV during NAC. In another study, Lee et al31 indicated that depression during NAC was a mediator in the relationship between resilience and health-related QOL in patients with BC, and QOL after NAC can be improved by screening and intervening for depression during NAC in patients with BC. Meanwhile, Takada et al29 reported that high QOL before chemotherapy was an independent factor in overall survival (table 3).

DISCUSSION
In recent years, NAC has been widely used in the treatment of BC, and its efficiency in early-stage BC is as high as 70%–90% and has improved the success rate of breast-conserving surgery and the long-term prognosis of patients in complete pathological remission.32 33 However, it also has significant side effects on various organs of patients. Patients with BC after NAC require further surgical treatment. Chemotherapy-related symptoms and poor QOL inevitably affect the patient’s surgical tolerance and it may delay the patient’s surgical treatment in severe cases.
The initial stages of treatment and the months following the end of treatment can be difficult times for patients, both physically and emotionally, and patients with BC are vulnerable to maladjustment and decreased QOL during these periods. Therefore, information about expected QOL will play an important role in the decision-making process of patients and clinicians considering NAC, so this study was conducted to systematically evaluate the QOL of NAC patients.

The results of this systematic review showed no significant change in overall QOL before and after NAC in patients with BC. However, during chemotherapy, patients’ QOL decreased, patients experienced increased pain, nausea and vomiting, dyspnoea and fatigue, and nausea remained unimproved despite the use of an antiemetic regimen that relieved vomiting. Patients’ QOL decreases during chemotherapy due to the toxic effects of chemotherapy drugs, and after chemotherapy, some of the toxic effects diminish and patients’ QOL improves. Emotional problems, such as anxiety and depression, are also aggravated during chemotherapy, but they all resolve at the end of chemotherapy.

Emotional problems during NAC showed a significant association with resilience before NAC. These findings are largely consistent with previous studies on QOL during NAC for other cancers, such as oesophageal cancer, rectal cancer, pancreatic cancer and muscle-invasive bladder cancer. A transient increase in physical symptoms and a decrease in QOL were seen after neoadjuvant therapy, and in those patients who underwent surgery, most domains returned back by several months. Different regimens of NAC have different aspects of impact on patients’ QOL. The regimen of doxorubicin, cyclophosphamide and docetaxel weekly had less distressing side effects compared with the 3-weekly group, and another regimen of paclitaxel and doxorubicin had fewer social well-being compared with weekly group. Comparisons of AC and PG regimens showed that PG had fewer physical adverse effects and AC had better psychological effects. Only one study of included studies compared the impact of NAC to adjuvant chemotherapy on BC patients’ QOL, both regimens could affect patients’ emotions. However, NAC was more damaging in the terms of physical, cognitive and personal performance due to more toxicity of the drugs in NAC. QOL can be improved in various ways, including appropriate interventions and enhanced social or family support. Past studies reported that women who are malnourished have a serious negative impact on QOL and nutritional intervention can improve the symptoms of nausea, vomiting, and loss of appetite in patients with BC, and exercise can reduce fatigue and improve the physical quality of patients with BC. Good nutritional status enables patients to better cope with intensive cancer treatment regimens. Patients with BC with high levels of social support have lower severity of chemotherapy-related symptoms. In addition, interventions can be based on QOL predictors of BC, such as chronotype, the level of QOL before chemotherapy and depression.

The limitations of this study are mainly in the low inclusion of literature on some subtopics and insufficient evidence, especially the contrast between NAC and adjuvant chemotherapy. This study suffered from publication bias and language bias and did not included some grey literature or unpublished, non-English language literature.

More original studies of high quality are needed. A potential area for further investigations provided by this systematic review is QOL in the perioperative and long-term postoperative periods after NAC. It is important to improve the long-term survival prognosis of NAC but also to focus on and improve QOL during and after NAC.

**CONCLUSION**

The results of this systematic review showed that BC patients’ QOL was significantly lower during NAC. There was no significant change in overall QOL before and after NAC. And this review found that the influences are mainly reflected in physical symptoms (80%), psychological effects (52%) and support from society or family (55%). QOL could be improved with appropriate interventions. Factors that affect QOL include chronotype, QOL before NAC and depression can affect the QOL. More
original research is needed in the future to understand
the profile and predictors of QOL in patients on neoadjuvant
therapy, which will help clinicians and patients make
better decisions and deal with NAC-related issues.

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Contributors YS is responsible for the overall content as guarantor, including study conducted, data accessed, and the publishing decision. YZ and XZ screened abstracts and full-text articles for inclusion. YZ and LC appraised study quality. Any disagreements or uncertainties during the screening and quality appraisal processes were resolved to YS. YZ drafted the manuscript, which was reviewed, edited, and approved by YS.

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


Supplementary: search strategies

Web of science Search strategy

#4 #1 AND #2 AND #3
#3 TS="Neoadjuvant chemotherapy"
#2 ((((((((TS="Quality of Life") OR TS="life quality") OR TS="QOL") OR TS="(HRQOL") OR TS="(Support") OR TS="(depress*)") OR TS="(anxiety") OR TS="(sexual*)") OR TS="(psychological") OR TS="(mental"
#1 (((TS="Breast Neoplasms") OR TS="(breast tumor") OR TS="(breast cancer") OR TS="(breast carcinoma")

Pubmed Search strategy

#8 #4 AND #5 AND #7
#7 #6 OR #2
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#5 #1 OR #3
#4 "Neoadjuvant Therapy"[MeSH Terms]
#3 "breast tumor"[Title/Abstract] OR "breast cancer"[Title/Abstract] OR "breast carcinoma"[Title/Abstract]
#2 "Quality of Life"[MeSH Terms] OR "Social Support"[MeSH Terms] OR "Depression"[MeSH Terms] OR "Anxiety"[MeSH Terms] OR "Sexuality"[MeSH Terms]
#1 "Breast Neoplasms"[MeSH Terms]
Embase Search strategy

#9 #6 AND #7 AND #8
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#7 'breast tumor'/exp
#6 #1 OR #2 OR #3 OR #4 OR #5
#5 'sexuality'/exp
#4 'depression'/exp
#3 'anxiety'/exp
#2 'quality of life'/exp
#1 'social support'/exp

Cochrane Library Search strategy

#9 #6 AND #7 AND #8
#8 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH descriptor:[Neoadjuvant Therapy] explode all trees
#6 MeSH descriptor:[Breast neoplasms] explode all trees
#5 MeSH descriptor:[Sexuality] explode all trees
#4 MeSH descriptor:[Depression] explode all trees
#3 MeSH descriptor:[Anxiety] explode all trees
#2 MeSH descriptor:[Social Support] explode all trees
#1 MeSH descriptor:[Quality of life] explode all trees
Scopus/PsyCINFO/CINAHL Search strategy

#4 #1 AND #2 AND #3
#3 "psychological" OR "mental" OR "anxiety" OR "depress*" OR "quality of life" OR "HRQOL" OR "QOL" OR "life quality" OR "sexual*" OR "support"
#2 "neoadjuvant chemotherapy"
#1 "breast cancer" OR "breast tumor" OR "breast carcinoma" OR "breast neoplasms"

Supplementary Table S1  Quality of RCT studies as assessed by Cochrane collaboration's tool for assessing risk of bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Random Sequence Generation (selection bias)</th>
<th>Allocation Concealment (selection bias)</th>
<th>Blinding of Participants and Personnel (performance bias)</th>
<th>Blinding of Outcome Assessors (detection bias)</th>
<th>Completeness of Reporting Outcome Data (attrition bias)</th>
<th>Selective Outcome Reporting (reporting bias)</th>
<th>other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker et al. [26]</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Souza et al. [27]</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Basen-Engquist et al. [28]</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
## Supplementary Table S2  Quality of cohort studies as assessed by Newcastle Ottawa Score (NOS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Representativeness of exposed cohort</th>
<th>Selection non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Outcome of interest</th>
<th>Comparability</th>
<th>Assessment of outcome</th>
<th>Length of follow up</th>
<th>Adequacy of follow up</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding et al.[20]</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Lee KM et al.[21]</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5</td>
</tr>
<tr>
<td>Takada et al.[29]</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>-</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Chellappan[22]</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Hermelink et al.[23]</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>-</td>
<td>-</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5</td>
</tr>
<tr>
<td>Rezapour et al.[24]</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>-</td>
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<td>7</td>
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<tr>
<td>Coelho et al.[25]</td>
<td>*</td>
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</tr>
<tr>
<td>Lee S et al.[31]</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>-</td>
<td>*</td>
<td>*</td>
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<td>*</td>
<td>6</td>
</tr>
</tbody>
</table>

## Supplementary Table S3  Quality of cross-sectional study as assessed by JBI Critical Appraisal Checklist

<table>
<thead>
<tr>
<th>Items</th>
<th>Aprilianto et al.[30]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Were the criteria for inclusion in the sample clearly defined?</td>
<td>N</td>
</tr>
<tr>
<td>2. Were the study subjects and the setting described in detail?</td>
<td>Y</td>
</tr>
<tr>
<td>3. Was the exposure measured in a valid and reliable way?</td>
<td>Y</td>
</tr>
<tr>
<td>4. Were objective, standard criteria used for measurement of the condition?</td>
<td>Y</td>
</tr>
<tr>
<td>5. Were confounding factors identified?</td>
<td>Y</td>
</tr>
<tr>
<td>6. Were strategies to deal with confounding factors stated?</td>
<td>N</td>
</tr>
<tr>
<td>7. Were the outcomes measured in a valid and reliable way?</td>
<td>Y</td>
</tr>
<tr>
<td>8. Was appropriate statistical analysis used?</td>
<td>Y</td>
</tr>
<tr>
<td>Overall appraisal</td>
<td>Include</td>
</tr>
</tbody>
</table>

Y: yes, N: no.