Immersive Virtual Reality for symptom management in breast cancer patients:a systematic review and meta-analysis of Randomized Control Trial

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Abstract

Design: A systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) 2020 Statement. It is registered in the Prospective Registry of International Systematic Reviews (PROSPERO) database. (Registration number: CRD42023447007).[PubMed, Embase, The Cochrane Library, Web of Science, CNKI, Wanfang Data Knowledge Service Platform, and Chinese Scientific and Technical Journal Database (VIP) were searched from the library's construction to August 1, 2023. Methods: After literature screening, data extraction, and evaluation of literature quality were independently performed by 2 researchers trained in evidence-based care according to the inclusion and exclusion criteria, and meta-analysis was performed using RevMan 5.4. Results: A total of 6 randomized controlled trials containing 531 patients were included. Meta-analysis showed that IVR-based interventions helped to improve anxiety symptoms [SMD=-2.06,95% CI= (-2.73,-1.40), P<0.0001], depressive symptoms [SMD=-2.31,95% CI=(-4.39,0.23), P=0.03] and fatigue symptoms [SMD=-1.94,95%CI=(-3.18,-0.71), P=0.002]; the qualitative analysis results showed that IVR technology could improve the pain and the quality of life of breast cancer patients, and the difference was statistically significant (P<0.05). Conclusions: IVR technology applied to breast cancer patients can improve their anxiety, depression, pain, fatigue, and other symptoms, and improve their quality of life, and it is interesting and worth promoting. Due to the limited number of included studies and sample size, more large-sample trials are to be conducted to explore the applicability and feasibility of IVR technology in symptom management of breast cancer patients and to validate the above results.

1 INTRODUCTION

The internationally recognized GLOBOCAN 2020 database[1]shows that in 2020, female breast cancer (BC) will for the first time overtake lung cancer as the most common cancer in the world and the leading cause of death in women. Due to the continuous progress of early screening, surgical treatment, adjuvant therapy and other technologies, the 5-year survival rate of breast cancer patients reaches 83.2%.[2] However, due to surgical trauma, postoperative radiotherapy and long disease duration, a series of complications, such as anxiety, depression, pain, sleep disorders, etc., are still inevitable, therefore, reducing the complications and improving the quality of life of breast cancer patients deserve our attention. Virtual reality (VR) technology is a non-invasive simulation technology with three-dimensional dynamic views generated in computer-generated images or environments, and the commonly used devices are head-mounted displays and headsets[3]. The commonly used devices are head-mounted displays and headsets. In recent years, virtual reality technology has been gradually applied to medical and healthcare systems due to its ability to provide a multi-sensory, immersive, interactive, motivational stimulation and feedback environment that is fun, safe, easy to operate, and easy to promote.[4] It has been gradually applied to medical and healthcare systems. Currently, there

have been several studies applying VR technology to the symptom management of certain diseases, such as Parkinson's disease[5] stroke, Alzheimer's disease[6,7] and chronic obstructive pulmonary disease (COPD)[8] etc., all of which have shown initial success. With the continuous development of VR, immersive virtual reality (IVR) is becoming more and more popular in clinical rehabilitation care. Compared with non-immersive and semi-immersive virtual reality technologies, IVR mobilizes multi-senses (vision, hearing, smell, touch, kinesthetic, proprioception) through an immersive experience, immersing patients in a three-dimensional dynamic The virtual environment in which the patient has immersed a three-dimensional dynamic view and physical behavioral interaction is more realistic and more able to mobilize the autonomy of the experience.[5] The IVR can be used in a variety of ways. Several studies have found that IVR can affect patients' cognitive dysfunction[9], pain[10], sleep disorders[11] and etc., but the results have not been harmonized. Currently, the effectiveness of IVR interventions for breast cancer patients is controversial, and previous studies[12] mainly evaluated the effects of non-immersive and semi-immersive VR technologies or included class experimental studies, and a systematic review of IVR for symptom management in breast cancer patients has not been reported.

2 | THE REVIEW

2.1 | Aims

This study aimed to evaluate the intervention effects of IVR technology on postoperative quality of life, negative emotions, pain, and fatigue in breast cancer patients in a randomized controlled trial, to seek higher quality evidence for clinical breast cancer rehabilitation.

2.2 | Design

This systematic review, meta-analysis, and meta-regression report comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13]. The systematic evaluation program is registered in the Prospective Registry of International Systematic Reviews (PROSPERO) database. (Registration number: CRD42023447007).

2.3 | Search methods

Computerized searches were performed on four English databases (PubMed, Embase, The Cochrane Library, Web of Science) and three Chinese databases (CNKI, Wanfang Data Knowledge Service Platform, and Wipu Chinese scientific and technical journal databases). The search time limit was from the establishment of the library to August 1, 2023, and relevant references and secondary literature were manually searched. A combination of subject terms and free words was used. English search terms included ""breast neoplasms, breast cancer, breast tumor, mammary neoplasm, mammary carcinoma, breast neoplasm, breast carcinoma breast malignan*, breast metastas*, mammary malignan*, mammary metastas*, Virtual Reality Exposure Therapy, virtual real*, VR, virtual-real*. virtual reality therap*, video gam*, computer gam*, gaming consol*, interactive gam*, Xbox, Playstation, nintendo, virtual environment*, virtual object*, virtual world*, virtual treatment*, virtual system*, virtual program*, virtual rehabilitation*, virtual therap*"; Chinese search terms include "virtual reality, virtual reality technology, virtual environment, virtual game, distraction, VR technology, interactive emotional simulation, virtual situation, breast cancer, breast tumor, breast cancer, breast cancer disease, breast tumor".

2.4 | Inclusion and exclusion criteria

The inclusion criteria of the literature were as follows: (a) Study subjects: female breast cancer patients whose diagnosis following the Breast Cancer Diagnostic and Treatment Guidelines and Norms of the Chinese Anti-cancer Association (2017 edition); age [?]18 years; (b) Type of study: study on the effect of the intervention of IVR technology on breast cancer; (c) Outcome indicators: anxiety, depression, quality of life, pain and fatigue; (d) Study design: a randomized controlled trial (RCT).

The exclusion criteria were as follows: (a) full text unavailable or missing original data; (b) duplicate publications; and iii) high risk of bias in the literature.

2.5 | Study selection

Notexpress 3.5 software was used to screen the retrieved results. Literature screening and data extraction were conducted independently by two researchers (the first and second authors) trained in evidence-based nursing according to the inclusion and exclusion criteria, firstly, initial screening of non-compliant literature based on the title and abstract, then reading the full text for further re-screening to determine the inclusion of the literature before the data extraction and cross-checking, and in case of disagreement, asking the third researcher (corresponding author) to collaborate in the adjudication, and in case of absence of full text or Incomplete data were obtained by contacting the authors.

2.6 | Search outcomes

Preliminary search of the database obtained a total of 1,244 pieces of literature, after reading the literature and the title of a total of 1,186 pieces of literature screened out, the remaining 58 pieces of literature, by reading the full text of the final inclusion of six pieces of literature, including five pieces in English and one in Chinese, a total of 531 patients, the specific literature included in the flow chart is shown in Figure 1.
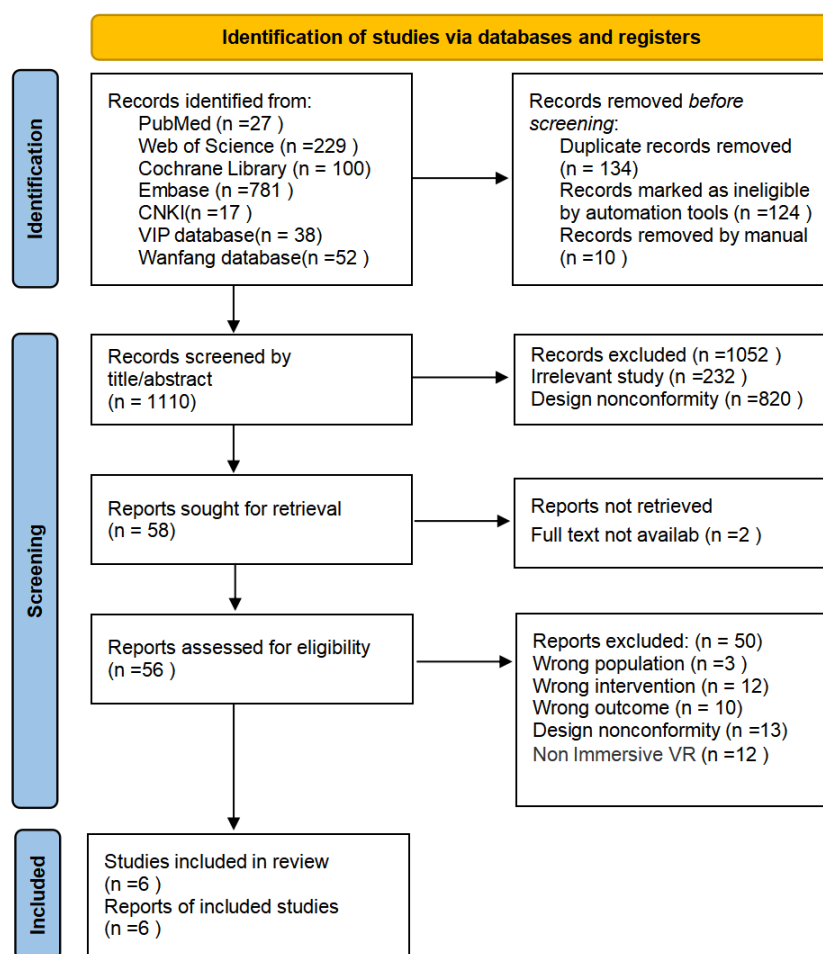

Figure1 PRISMA flow diagram

2.7 | Quality appraisal

The quality of the included randomized controlled trials was independently evaluated by 2 investigators

(first and second authors) using the Cochrane Handbook (5.1) Risk of Bias Assessment Tool, and a third investigator (corresponding author) was asked to adjudicate collaboratively in case of disagreement. Among them, the RCT evaluation tool included 7 entries, which were: generation of randomized sequences, allocation concealment, blinding of study subjects and interveners, implementation of blinding by outcome measures, loss to visit, selective reporting, and other biases.

2.8 | Data abstraction

Literature extraction information included: the first author, year of publication, author's country, study population, inclusion criteria, sample size, IVR platform, intervention method, implementation period, and outcome indicators.

2.9 | Synthesis

The meta-analysis will be conducted using RevMan 5.4.Since the outcome indicators in this study are all continuous variables and the assessment tools for the outcome indicators are different, the standard mean difference (SMD) was chosen as the effect indicator and its 95% CI is provided.When SMD is used, if the direction of the unit of measure is opposite between the scales, the Measurement means of the corresponding scales were multiplied by -1 so that all scales had the same unit of measure orientation. The χ^2 test and I^2 statistic were used to determine the heterogeneity of the included studies. If P ¿0.1 and I^2 <50%, it indicated that the heterogeneity was small and a fixed-effects model was selected for the analysis; if P [?] 0.1 and I^2 [?] 50%, it indicated that there was a significant heterogeneity, and further judgment was needed to determine the source of the heterogeneity, and a random-effects model was selected for the analysis after eliminating the interference of significant clinical heterogeneity. Clinical and methodological heterogeneity was handled by subgroup analysis and sensitivity analysis, or descriptive analysis.

3 | RESULTS

3.1 | The search results

Preliminary search of the database obtained a total of 1,244 pieces of literature, after reading the literature and the title of a total of 1,186 pieces of literature screened out, the remaining 58 pieces of literature, by reading the full text of the final inclusion of six pieces of literature, including five pieces in English and one in Chinese, a total of 531 patients, the specific literature included in the flow chart is shown in Figure 1.

3.2 | Basic characteristics of the included literature and quality evaluation results

Six randomized controlled trials were included[14-19] Of these, three were in patients with breast cancer chemotherapy[16, 18, 19], one in patients with breast cancer radiotherapy[15], and one in patients with metastatic breast cancer[17]. Of these, all studies had comparable baseline information, three reported methods of allocation concealment, and five described sample attrition. The results of this literature quality assessment showed that 1[15] quality grade of A and the remaining 5[14, 16-19] quality grade of B. The overall quality of the literature was moderate. The basic characteristics of the included literature are shown in Table 1, and the evaluation of literature quality is shown in Figure 2.

Table 1 Characteristics of the included studies (n=6)

Author/Year	nations	Research design	Subject of study (I/C) crowds
Cao/2023[14]	sino	Two-arm RCT	High mortality anxiety Stage I-III breast cance
Shin MD/2023[15]	South Korea (Republic of Korea)	Two-arm RCT	Breast Cancer Radiotherapy
Zhang/2022[16]	sino	Two-arm RCT	Breast Cancer Chemotherapy
Chirico/2019[18]	Italy	Three-arm RCT	Breast Cancer Chemotherapy
Mohammad/2018[19]	Arabian	Two-arm RCT	Breast Cancer Chemotherapy
Reynolds/2022[17]	New Zeeland	Two-arm RCT	metastatic breast cancer

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Table 2 continued

Author/Year	Trial group interventions
	Specific measures
Cao/2023[14]	VR United Minds
Shin MD/2023[15]	Receive virtual reality-based explanations of radiotherapy procedures in addition to standard informa
Zhang/2022[16]	VR-CALM, immersion in landscapes such as the seaside and Butterfly Valley, where patients can wal
Chirico/2019[18]	Immersive and interactive virtual reality
Mohammad/2018[19]	drug + virtual reality sessions.
Reynolds/2022[17]	Virtual environment "Happy Place + Ripples", home intervention, measured at 6 different time point

Note: Quality of life Anxiety Depression Pain Fatigue Sleep disorders Cognitive function Satisfaction Stress Hypercaloric screen symptom Radiation therapy knowledge acquisition Stress;

RCT: randomized controlled trial; T is the test group, C is the control group; T-DAS: death anxiety scale; EORTC QLQC30: European Organization for Research and Treatment of Cancer Quality of Life Scale; APAIS: Amsterdam Preoperative Anxiety and Information Inventory; STAI: State-Trait Anxiety Inventory; LASA: Linear Analog Scale Assessment; FACT-B: FACT-B: Life of the Breast Cancer Patient Quality Measurement Scale; DT: Pressure Thermometer; CARS: Cancer Recurrence Fear Scale; PFS: Piper Fatigue Scale; PSQI: Pittsburgh Sleep Quality Index; SAS: Self-Anxiety Scale; SDS: Self-Rated Depression Scale; SAI: State Anxiety Inventory; SV- POMS: Brief Mood State Profile; VRSQ: Virtual Reality Symptom Questionnaire; VAS: Visual Analog Scale for Pain; MMSE: Mini-Mental State Examination; EQ-5D-5L: European Five-Dimensional Health Scale; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue Scale; BPI: Brief Pain Inventory, DASS-SF: Depression, Anxiety and Stress Scale.
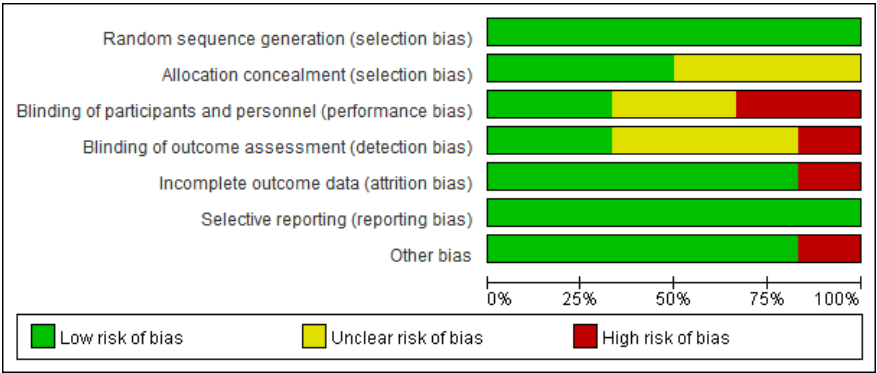

Figure 2 Quality assessment of the included studies.

3.2 | Results of meta-analysis

Due to significant heterogeneity between groups, anxiety, depression, and fatigue will be selected for meta-analysis, and pain and quality of life for descriptive analysis.

3.2.1 | Anxiety meta-analysis

Of the six studies included, four studies[14, 16, 18, 19] reported the effect of IVR techniques on anxiety in breast cancer patients, and 3 studies[16, 18, 19] focusing on breast cancer chemotherapy patients and choosing a random-effects model, showed that IVR relieved patients' anxiety compared to the control group, with a statistically significant combined effect size [I^2=79%, SMD=-2.06,95% CI=(-2.73,-1.40),P<0.0001] (Figure 3). Sensitivity analysis was performed using a literature-by-literature exclusion approach, when excluding

Chirico et al.[18] , Cao et al.[14] 's studies, the heterogeneity decreased significantly and the difference was statistically significant [I^2 =16%, SMD=-1.52, 95% CI=(-1.88,-1.15), P<0.0001] (Figure 4). The heterogeneity may be related to the different measurement tools, study populations, and intervention durations.
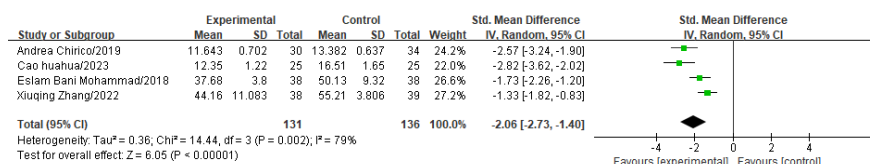

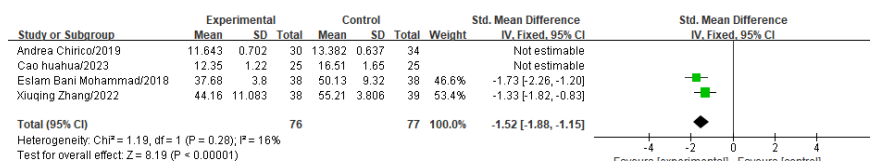Figure 3 Effects of IVR-based interventions on anxiety.

Figure 4 Effects of IVR-based interventions on anxiety (Exclusion of 2 studies).

3.2.2 | Depression meta-analysis

Three studies[16-18] respectively, exemplified the effect of IVR on depression in breast cancer patients, and the results showed that IVR-based interventions were effective in alleviating depressive symptoms [SMD = -2.31, 95% CI = (-4.39,0.23)](Figure 5) compared to the control group, with a statistically significant difference (p < 0.05), but with a high degree of heterogeneity (I^2 = 97%). After excluding the Chirico et al.[18] 's study, the combined effect size was statistically significant and heterogeneity decreased significantly [I^2 =35%, SMD=-0.68, 95% CI=(-1.09,-0.27), p=0.001](Figure 6). Heterogeneity may be related to treatment duration and intervention period.
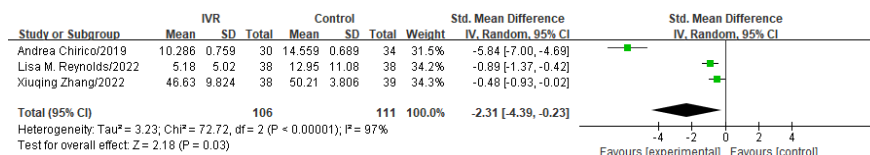

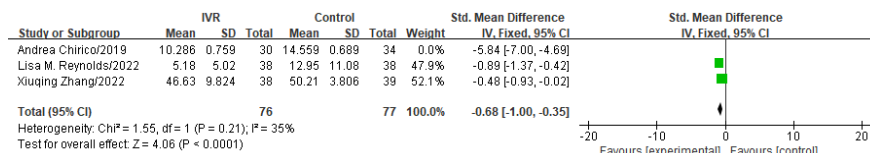
Figure 5 Effects of IVR-based interventions on depression.

Figure 6 Effects of IVR-based interventions on depression (Exclusion of 1 study).

3.2.3 | Fatigue meta-analysis

Three studies[16-18] describing the effect of IVR on fatigue in breast cancer patients included a total of 179 study participants, and the results showed a statistically significant combined effect size for the IVR-based intervention compared to the control group [I^2 =93%, SMD=-1.94, 95% CI=(-3.18,-0.71),P=0.002](Figure

7). Sensitivity analyses were performed using a literature-by-literature approach, and when Reynolds et al.[17] 's study, the heterogeneity disappeared (I^2 =0%), and meta-analysis using a fixed-effects model showed that the difference was statistically significant [SMD=-2.53,95% CI=(-2.98,-2.08),P<0.00001](Figure 8). The heterogeneity may be related to the measurement tool, the intervention period and the location of the intervention.
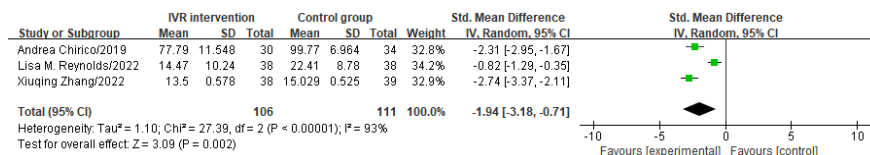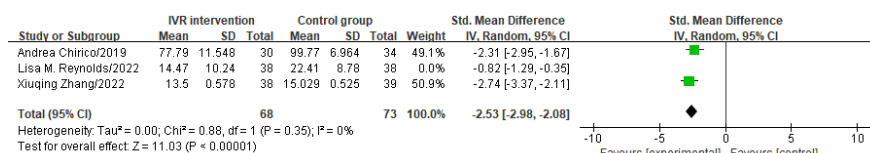

Figure 7 Effects of IVR-based interventions on fatigue.

Figure 8 Effects of IVR-based interventions on fatigue (Exclusion of 1 study).

3.2.4 | Pain analysis

Two studies[17, 19] have investigated the effect of IVR technology on pain in breast cancer patients, and the results showed that after the intervention of IVR technology, one study[19] of VAS pain scores decreased from 7.32 to 0.33, with a significant reduction in pain compared with the pre-intervention level, and the pain scores of the test group with IVR combined with medication were lower than those of the control group with medication for pain relief alone after the intervention, and the difference was statistically significant ($P <$ 0.05). Another study[17] found that VAS pain scores decreased in the test group through the IVR technique intervention, and the difference was statistically significant ($P < 0.05$).

3.2.5 | Quality of life analysis

Three studies[14, 16, 17] reported the effects of IVR technology-based interventions on the overall quality of life of breast cancer patients, and two studies[14, 16] found that after intervening on breast cancer patients through IVR combined with psychological care, the quality of life scores of patients in both groups were higher than before intervention, and the experimental group was higher than the control group, which was a statistically significant difference; another study[17] on the other hand, intervened on metastatic breast cancer patients through IVR technology, and the results showed that the quality of life scores of patients in both groups improved less, but the difference was still statistically significant ($P < 0.001$).

4 | DISCUSSION

This paper evaluates the effectiveness of IVR technology-based intervention for breast cancer patients through meta-analysis, and the results show that the study participants' symptoms of anxiety, depression, pain, and fatigue were alleviated, and their quality of life was improved, and the difference was statistically significant.

With the transformation of the biopsychosocial medical model, the impact of negative emotions on breast cancer patients has attracted more and more attention. Postoperative breast loss, wound pain, worry about disease prognosis, nausea and vomiting due to chemotherapy, hair loss, etc. can cause anxiety, depression and other adverse psychological symptoms, which can seriously affect the prognosis and regression of patients[20]. The results of this study showed that Reynolds et al.[17] study concluded that the intervention effect of IVR technology on anxiety in breast cancer patients was not significant, probably because the study subjects

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reported lower levels of anxiety before the intervention, resulting in no significant difference between before and after the intervention; the rest of the studies reported that IVR had a significant improvement in anxiety and depression symptoms in breast cancer patients, which was consistent with the meta-analysis of the effect of the relevant VR interventions on breast cancer.[21] The results are consistent with the fact that the principle of action may be to utilize the distraction mechanism. In the study included in this paper, the researchers based on IVR technology, immersed patients in wonderful natural scenery such as the sea, forests, waterfalls, etc., and cooperated with breathing and movements to stretch the body and mind and achieve a state of relaxation, to achieve the purpose of alleviating anxiety in breast cancer patients by distracting attention from the disease and the medical environment in which they live. And Zeng et al.[22] 's meta-analysis of cancer patients showed that VR-based interventions did not have a significant effect on anxiety relief. The reason for this may be that although non-immersive VR technology uses virtual scenes, it is mainly connected to the virtual environment through the computer screen, and the patients are not detached from the real world and are not in it, so the authenticity and fun are not as good as immersive virtual reality technology, and may be affected by the hospital environment and other factors, so the patients cannot completely relax their bodies and minds to achieve the effect of relieving anxiety.

It has been found that fatigue, with a prevalence of about 90% in breast cancer patients, is one of the most common and serious complications in breast cancer patients and is often not effectively treated[23] , which may be affected by adverse reactions such as nausea, vomiting, loss of appetite and bone marrow suppression produced by chemotherapy; and fatigue will aggravate patients' negative emotions such as anxiety and depression, which will aggravate their physical and mental burdens and further affect their quality of life. Some studies have observed postoperative breast cancer patients and found that sleep deprivation aggravates pain, while good sleep promotes wound healing and tissue repair[24] . The results of this study showed that interventions based on IVR technology can improve fatigue symptoms in breast cancer patients, which is consistent with Cheng et al.[25] class experimental study results, but different from Burrai et al.[11] The results of meta-analysis of IVR-based interventions for cancer chemotherapy patients, the reasons for this difference may be (1) the small sample size of the included studies; (2) due to the nature of the virtual reality, blinding could not be implemented for all interventions, so it may lead to bias, and the limited number of the included studies did not allow for the analysis of the source of the bias through the funnel plot; and (3) the period and frequency of the interventions in the included studies, varied greatly between control groups.

Postoperative pain is one of the most common complications of breast cancer, and studies have shown that about 25% to 60% of patients will develop chronic pain that lasts for 7-12 years, which can cause the body to produce autonomic responses, such as increased heart rate, increased blood pressure, nausea and vomiting, which seriously affects the quality of life of breast cancer patients.[26] Currently, non-pharmacological interventions to control pain through IVR technology are receiving increasing attention, and its mechanism of action may be focus shifting, when the patient is immersed in the virtual environment, the attention will be shifted away from the painful stimuli, and in this way, weakening its responsiveness to injurious neural signals, and thus pain perception decreases.[27] Of the studies included in this paper, Mohammad et al.[19] intervened in breast cancer chemotherapy patients through immersive virtual environments, such as deep-sea diving in the Ocean Rift Valley, combined with morphine medication for pain relief, and after 4 months of intervention, the results showed that compared to medication alone for pain relief, the IVR-based intervention combined with medication was more effective in relieving pain, and the side effects of the medication, such as nausea, vomiting, and constipation, were significantly reduced; Reynolds et al.[17] An at-home IVR intervention that allowed patients to pile rocks on a waterfall, jump in a mountain range, and write on a beach showed significant pain reduction after four weeks of intervention, with pain relief lasting for at least 48 hours post-intervention. Although evidence suggests that IVR is effective in relieving immediate or short-term pain, the long-term effects have not been proven, and more high-quality studies need to be included in the future to determine the long-term efficacy of IVR techniques for breast cancer pain.

5 | LIMITATIONS

There are still some limitations in this meta-analysis, firstly, due to the novelty of IVR technology, there

are fewer high-quality randomized controlled trials based on IVR technology, and the intervention time is not very long, so the sample size of the included studies is relatively small, and a large number of studies will be needed in the future to explore the effects of the long-term interventions; secondly, only literature published in both Chinese and English was included, which is limited in number, and may be limiting for the comprehensiveness of the results; thirdly. Most of the IVR devices were not developed and designed specifically for breast cancer patients and may not have fully realized their intervention effects; fourth, some studies reported that some patients experienced screen sickness symptoms such as nausea, vomiting, and vertigo[16] and claustrophobia in some patients[17]. Fourth, some studies have reported that some patients experienced screen sickness such as nausea, vomiting and vertigo, and some experienced claustrophobia.

6 | CONCLUSION

This systematic review shows that IVR technology applied to breast cancer patients can improve their symptoms such as anxiety, depression, pain, and fatigue, and enhance their quality of life, and is fun and worth promoting. However, due to the limitations of this paper, we expect that in the future, we can form a professional team including breast specialists, nurses, counselors and programmers and other people to develop devices and games specifically for breast cancer patients, and carry out a large-sample trial on symptom management and rehabilitation of breast cancer patients, to explore its applicability and feasibility in breast cancer patients, and to validate the above results.

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