Effectiveness of virtual reality technology in symptom management of end-of-life patients: protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction With the worsening of population ageing globally, the number of the elderly with chronic and incurable diseases such as malignant tumours is gradually increasing, and the need for palliative care is growing. As a primary task in the end-of-life phase, symptom management is an essential aspect of palliative care, which aims to alleviate distressing symptoms of terminally ill patients and improve their quality of life. Virtual reality (VR) technology, which allows the creation of simulated environments in which a three-dimensional experience is generated, has been increasingly used in palliative care for symptom management. Therefore, we aim to conduct a systematic review to investigate the effects of VR-based interventions on end-of-life patients.

Methods and analysis This protocol for conducting a systematic review and meta-analysis will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. We will conduct a series of searches from inception to 31 July 2022 in the following databases: PubMed, Embase, Web of Science, the Cochrane Library, JBI, EBSCO, CNKI, Wanfang and SinoMed. The key concepts of ‘virtual reality’ and ‘end-of-life’ will be combined in each database using both free-text terms and controlled vocabulary terms (eg, MeSH/Emtree terms), if available. Two independent reviewers will use raw data to explore the effectiveness of VR for symptom management in end-of-life patients. The Cochrane Risk-of-Bias tool will be used to assess the risk of bias of included studies. Disagreements will be resolved by a third independent reviewer to reach a consensus. For the included articles, Review Manager software will be used for data synthesis and I2 statistics will be used to measure the heterogeneity. Subgroup analyses and sensitivity analyses will be used to identify the source of heterogeneity.

Ethics and dissemination As this is a protocol for a systematic review and meta-analysis, patients will not be included in this study. For this reason, ethical approval is not required. In order to disseminate the research findings, the results and conclusions of this review will be submitted to a worldwide journal.

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INTRODUCTION

As the global population ages,1 the incidence and mortality of chronic diseases such as malignant neoplasm and cardiovascular diseases remain high,2 and the number of patients suffering from incurable diseases increases year by year.3 Patients are identified to be at the terminal stage if they have an estimated survival of 6 months or less.4 Palliative care is an interdisciplinary approach, defined as care that provides relief from pain and other symptoms and supports quality of life for patients with serious advanced illness and their families.5 According to the WHO, more than 56.8 million people worldwide are in need of palliative care each year, including 25.7 million in the last year of their lives.6 For them, the control of misery and discomfort symptom has become their primary needs instead of curative treatment. Symptom management has become a key measure to improve the quality of life for patients with advanced stage of disease.7

As the disease progressively worsens, terminally ill patients often experience a significant symptom burden, contributing to the impaired quality of life. Although the pathological mechanisms vary from disease to disease, most end-stage patients share the same symptoms, such as pain, fatigue, dyspnoea, nausea and vomiting, distention oedema.8 Meanwhile, the coexistence
of multitype painful symptoms exerts huge agony on end-stage patients. In addition to physical symptoms, patients have to face many factors in the process of disease treatment, such as the impact of poor prognosis, lack of curative treatment, physical deterioration, social role transformation and financial burden. End-stage patients are prone to psychological distress such as anxiety and depression, and psychological discomfort in turn increases the burden of physical symptoms. Consequently, terminally ill patients face both physical and psychological stress.

With continuous technological innovation and rapid advances in digital medicine, virtual reality (VR) creates a computer-generated environment in which scenes and objects appear to be real, making users feel as if they are immersed in real surroundings. This technology has been used as a burgeoning therapy to manage the psychological and physical symptoms of patients with cancer, including pain, anxiety and fatigue. VR is based on the use of computer technology, using visual graphics, sound and other sensory inputs to create an interactive virtual scene with immersive, interactive and imaginative characteristics. Current VR systems include head-mounted displays (HMDs) and 3D-enabled glasses, as well as other devices including headsets for noise cancellation, head and/or body-tracking sensors, and other input hardware such as joysticks and data gloves. The main principle of VR technology is to distract the patient’s attention from his/her current clinical situation by stimulating the visual cortex while engaging the other senses. Dispersing patients’ attention to the real world can relieve discomfort symptom, especially pain and anxiety. Studies have proved the applicability of VR technology as an adjuvant therapy in terminally ill patients to relieve pain, anxiety and depression. Austin et al used 3D HMD VR for 13 patients undergoing a palliative care intervention, which showed improvements in pain, dyspnoea, nausea, loss of appetite and increased well-being. Moscat et al conducted a 4-day home VR intervention with an average use time of 55 min in 14 patients with advanced cancer, and the results showed that after using a one-time VR intervention, the symptoms of pain, fatigue, drowsiness, shortness of breath, depression, anxiety and dyspnoea in patients with advanced cancer were reduced, which is consistent with the findings of Niki et al.

At present, studies have proved the feasibility of VR technology in terminal ill patients, and preliminary exploration has also been made on the application of VR technology in end-of-life patients. However, there is no clear evidence on whether VR technology is effective for end-of-life patients and whether it can help end-of-life patients to reduce the burden of symptoms. To the best of our knowledge, few systematic reviews have paid attention to the effectiveness of VR applications in terminal patients. Therefore, to fill this gap, we will summarise and systematically evaluate clinical intervention trials of VR applied to end-of-life patients, and provide new evidence for the symptom management of end-of-life patients through knowledge synthesis, aiming at improving the quality of life of terminal patients.

OBJECTIVES
The primary objective and meta-analysis of this systematic review is to assess the effectiveness of VR technology in the management of physical and psychiatric symptoms among end-of-life patients and to characterise VR technology interventions that can alleviate end-of-life symptoms.

METHODS AND ANALYSIS
Study design registration
This systematic review and meta-analysis protocol will be reported in accordance with the recommendations of the revised Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. This protocol was registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under the registration ID CRD42022344679.

Eligibility criteria for study selection
Types of participants
We will focus on end-of-life patients aged ≥ 18 years, regardless of disease type, race, ethnicity or cultural identity.

Types of studies
We will include experimental studies including randomised controlled trials, quasiexperimental studies and case controlled studies.

Types of interventions
To obtain comprehensive studies and reduce selection bias, we will select all trials assessing VR-based interventions. In the trials, the selection process will not be based on the type or nature of the VR-based intervention (immersive and non-immersive virtual environments).

Types of controls
We will select only studies that present a control group, such as standard control group, blank control group, attention control group or waiting-list control group.

Outcome measure
Outcome measures will be associated with symptoms in end-of-life patients and will be divided into physical and psychological symptoms. Physical symptoms include pain, fatigue, vomiting, dyspnoea, nausea, sleep disorders and loss of appetite. Psychological symptoms include anxiety, depression and satisfaction.

Inclusion criteria
Inclusion criteria are: (1) patients with an expected survival ≤ 6 months or undergoing palliative care; (2) VR technology applied in the intervention; and (3) randomised controlled trials, quasiexperimental studies and case controlled studies.
**Exclusion criteria**

Studies will be excluded if they: (1) describe only the technology and (2) are literature reviews, posters, comments, letters, study protocols or proceedings papers.

**Search strategy**

**Electronic data**

The following electronic databases will be consulted for articles published until July 2022: PubMed, Embase, Web of Science, Cochrane Library, JBI, EBSCO, CNKI, Wanfang and SinoMed. Within each database, the key concepts of ‘virtual reality’ and ‘end-of-life’ will be combined together, using both free-text terms and controlled vocabulary terms (eg, MeSH, Emtree terms), if available. Details of the search strings in PubMed database are shown in [table 1](#).

**Search for other resources**

A snowball method will be used to search the reference lists of selected articles for reading and reference for a broader literature review. To minimise publication bias, the Open Grey online database will be used to search grey literature. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform will be searched for on-going registered trials. If the clinical trial retrieved has published relevant articles, we will check whether the articles have been included; if they have been included, they will be excluded as duplicate literature. Otherwise, it will be included in the selected articles. If the clinical trial retrieved has not published relevant articles, the experiment may be in progress. If the author uploads the data, we will include it in the study; if the author does not upload the data, we can wait for the author to update or try to contact the author.

**Study selection**

The search results will be retrieved and duplicates will be deleted using NoteExpress. First, two reviewers (WX and FC) will read 3–6 articles for preliminary browsing. Second, they will jointly standardise and unify the evaluation methods. Third, the titles and abstracts of all retrieved articles will be independently screened by the two reviewers based on the predetermined inclusion/exclusion criteria. Articles that do not pass the title and abstract screening will be further rescreened and evaluated in their entirety to determine the eligibility of the article. If any disagreement arises during the literature screening process, a third independent reviewer (XX) will discuss it or consult with experts in the field of palliative care to reach a consensus.

**Data extraction**

The data extraction will be completed by two reviewers. They will independently extract data from the included studies and cross-check the extracted data. Included literature will be extracted into an Excel spreadsheet including the first author, the year of publication, the type, the study object, the intervention, the outcome indicators and the main conclusions of the included studies.

**Dealing with missing data**

If the full text is not available or there are missing data in the article, we will attempt to contact the authors by email. If the author does not respond or is unable to provide missing data, we will choose the complete case analysis and the last observation carried forward. If data are missing at random, we will take a full case study approach where only individuals who have completed the study will be included. For longitudinal studies, we will adopt the last observational propulsion method, replacing the missing final result with the last observation before the participant exits. In addition, if possible, sensitivity analyses will be performed to assess how sensitive the results are to reasonable changes in the assumptions made. In the discussion, the potential impact of missing data on the final outcomes of the review will be elucidated.

**Risk-of-bias appraisal**

Included studies will be assessed by two postgraduate nursing students, and the entire evaluation process will be supervised by their postgraduate supervisor engaged in palliative care. Seven domains assessing risk of bias as stipulated by the Cochrane Collaboration Group will be used, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. Evaluation results include three types: low risk of bias, high risk of bias or unclear, and these results will be inputted into the Review Manager software (RevMan, V.5.4. the Cochrane Collaboration, 2020). Any differences between reviewers will be resolved through discussion or by a third investigator.

**Data synthesis and statistical analysis**

**Data synthesis**

We will use RevMan for data synthesis. Considering that the results will be measured with different validation scales, we will calculate the standardised mean differences and 95% CIs for continuous variables. P value of <0.05 will be considered statistically significant. We will use forest plot for analysis.
Assessment of heterogeneity
We will use the $I^2$ statistic to measure heterogeneity between trials in each analysis. We will use these ranges to guide our interpretation of the $I^2$ statistic in accordance with section 10.10.2 of the Cochrane Handbook for Systematic Reviews of Interventions. If $I^2=0\%–40\%$, heterogeneity will not be significant. If $I^2=30\%–60\%$, it may represent moderate heterogeneity. If $I^2=50\%–90\%$, it may represent substantial heterogeneity and if $I^2=75\%–100\%$, it will indicate considerable heterogeneity.

Statistical analysis
For the assessment of symptoms, the measurement tools used by different authors may vary. Taking pain symptoms as an example, different authors will use different measurement tools such as the visual analogue scale, the numerical rating scale and the Brief Pain Inventory-Short Form. Therefore, if the measurement tools for the derived metrics are the same, statistical analysis will be performed using mean deviations. If the measurement tools are different, the standard mean difference will be used. To synthesise the data, when the statistical heterogeneity is not significant ($I^2<50\%$), a fixed effects model will be selected. The fixed effects model means that we assume that the true effect of the VR intervention effect is the same in every study, and that the observed differences between studies are due to chance. We will use the Mantel-Haenszel method, which is the default fixed-effect methods of meta-analysis programmed in RevMan. When the statistical heterogeneity is significant ($I^2\geq50\%$), a random effects model (DerSimonian and Laird method) will be selected, followed by further analysis to determine the cause of heterogeneity. Subgroup analyses and sensitivity analyses will be performed to identify the sources of heterogeneity. Finally, if the heterogeneity is considerable high ($I^2>75\%$), a narrative description will be applied.

Subgroup analysis
When heterogeneity is evident ($I^2>50\%$), subgroup analyses will be used to explore the source of heterogeneity. Subgroups will include end-of-life patients with different diseases, different types of VR systems, different duration of interventions and different general information such as age, gender, education level, etc. If analyses within each subgroup are performed using fixed-effect models, then these statistics will relate to differences in typical effects across subgroups. If analyses within each subgroup are performed using random effects models, then these statistics will relate to the variation in the mean effects in different subgroups.

Sensitivity analysis
Sensitivity analyses will be conducted at our discretion to identify the source of heterogeneity. We will gradually weed out the low-quality studies, re-estimate the pooled effect sizes and compare the results with those of the meta-analysis before the exclusion to explore the impact of the study on the pooled effect sizes and the robustness of the results. If there is no significant change in the results after exclusion, it indicates that the sensitivity is low and the results are relatively stable and credible; conversely, if the exclusion yields a largely different or even diametrically opposed conclusion, this indicates a high sensitivity and low robustness of the outcome. Therefore, the interpretation of these results and conclusions should be very cautious, as it suggests that there are important and potential bias factors related to the effectiveness of the intervention, and the source of the controversy needs to be further clarified.

Publication bias
Studies with statistically significant findings will be more likely to be published than non-statistically significant studies. Therefore, during the literature search, we will identify publication bias by egger’s regression test or funnel diagram and collect data from all studies. If the distribution is symmetric, it indicates no publication bias. Multiple publication bias arises if observations from the same group of subjects are divided into two or more publication papers, and we will control the publication bias by including this group of subjects only once.

Patient and public involvement
No patient involved.

Discussion
Patients at the end of life often face great physical suffering. Seow et al found that in the last month of life, the prevalence of physical symptoms would increase in all patients, among which moderate and severe pain, loss of appetite, dyspnoea and other symptoms were particularly common. Consistent with the common painful symptoms of advanced cancer noted by Henson et al, therefore, high-quality symptom management can help patients with terminal stages to reduce suffering and improve their quality of life.

VR technology is a form of distraction therapy that allows patients to temporarily immerse themselves in a calm, pleasant and beautiful environment in order to alleviate their pain. Niki et al helped end-stage patients realise their wish of ‘going to an unforgettable place’ or ‘going home’ through VR technology, which not only improved the burden of patients’ symptoms but also met their needs, to improve the patient’s symptom burden while meeting the patient’s needs. At present, with the continuous development of science and technology, VR is increasingly applied to patients with cancer, burn patients, clinical teaching, etc, providing a new way of thinking for the symptom management of end-stage patients. The feasibility of VR application in symptom management of end-stage patients has been
confirmed, and more and more new evidence has emerged. Therefore, our aim is to further demonstrate the effectiveness of VR for symptom management in end-stage patients, with the hope of forming best practice evidence to guide future clinical work.

**Ethics and dissemination**

This study does not require ethical approval because it is based on a review of published studies and does not include any intervention in humans or animals. We will not endanger the privacy of individuals or compromise their rights. The findings of this study will be submitted to a peer-reviewed journal for publication.

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**Contributors** WX is the first author and registered the protocol in the PROSPERO database. XX obtained funding, critically reviewed the protocol and contributed to the drafting of the final manuscript. WX and FC collected and analysed the data. YC, XL and MY revised and reviewed this article. All authors have read and approved the final manuscript. WX and XX are the guarantors of the study.

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**Competing interests** None declared.

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**REFERENCES**

22 Ong T, Prescott J. Implementations of virtual reality for anxiety-related disorders: systematic review. *JMR Serious Games* 2018;e10065.


