

## Translating Evidence for Clinical Practice in the Management of Psychological Distress in Patients with Advanced Oncology

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#### Abstract

Objective: To explore the nursing management of psychological distress in patients with advanced cancers based on the best evidence and evaluate the effect of its application. Methods: 153 patients with advanced cancers admitted to the oncology department of a tertiary-level hospital in Hubei Province from January to December 2024 were selected as the study subjects, and 79 patients with advanced cancers admitted from April to June 2024 were selected as the baseline group and 74 patients with advanced cancers as the evidence-based practice group. Using the "evidence-based continuous quality improvement model" as a guide, the evidence-based practice of psychological distress management was applied to patients with advanced cancers according to the four stages of evidence acquisition, current status review, evidence introduction and effect evaluation, and the changes in the incidence rate of psychological distress were compared before and after the application of the evidence-based practice. Results: Nineteen pieces of evidence on hospice management of psychological distress in patients with advanced oncology were summarised, and the evidence was translated into 13 review indicators for evidence-based practice. The implementation rate of the review indicators for the management of psychological distress in patients with advanced oncology and the level of nurses' knowledge, attitudes, and behaviours related to psychological distress in patients with advanced oncology were significantly improved, with statistically significant differences in the knowledge and behavioural dimensions (P < 0.05). The incidence of moderate to severe psychological distress in patients with clinically advanced cancers was reduced from 76% to 43.5% (P = 0.04). Conclusion: Evidence-based nursing practice of hospice management of psychological distress in patients with advanced cancers can effectively improve the clinical practice environment, improve nurses' knowledge of prevention of psychological distress in patients with advanced cancers, attitudes and adherence to clinical

measures, reduce the incidence of moderate-to-severe psychological distress in patients with advanced cancers in the clinic, and improve the quality of their lives.

#### **Keywords**

Advanced Cancers, Psychological Distress, Evidence-Based Care, Evidence Application

## 1. Introduction

According to data from the International Agency for Research on Cancer (IARC) [1], in 2020, China will have the highest number of cancer deaths and incidence cases in the world. Cancer is now one of the leading causes of death in China. With the deterioration of the disease, advanced cancer patients have to suffer from severe symptoms and adverse effects of treatment, and will face the threat of death at any time, which is very easy to produce great psychological distress [2]. With the transformation of medical care model, national policies and oncology carerelated guidelines encourage healthcare professionals to pay attention to the psychological needs of patients. Studies have shown that the psychological distress of advanced cancer patients is more difficult to be recognised by healthcare professionals than their physical symptoms, and there is a lack of evidence-based hospice management for the assessment of psychological distress in advanced cancer patients [3]. In order to promote evidence-based clinical translation and enhance the quality of clinical care, the evidence-based continuous quality improvement model diagram, which provides an effective way and method for the localised application of evidence by promoting the translation of evidence to the clinic, can effectively promote the continuous improvement of the quality of clinical care. Based on the prevalence of psychological problems in patients with advanced lung cancer, the transformation of medical care models, and the effectiveness of evidencebased care in addressing psychological problems, this study summarised the current best evidence, carried out the application of evidence translation, and adopted the evidence-based continuous quality improvement model developed by the Centre for Evidence-Based Nursing at Fudan University [4], which was carried out in accordance with the four phases of evidence acquisition, review of the current status quo, introduction of evidence, and evaluation of the effect of evidence translation, which provides reference for nursing staff to adopt effective management strategies. The project was approved by the Hospital Ethics Committee.

#### 2. Material and Methods

#### 2.1. Access to Evidence

#### 2.1.1. Subject

According to PIPOST, the initial question of evidence-based nursing was formed

[4], *i.e.* P (Population, target population for evidence application): advanced oncology patients assessed for psychological distress. I (Intervention): screening, assessment, response, referral, follow-up. P (Professional, professionals applying evidence): clinical nurses. O (Outcome, indicators of the project): (structural indicators) at the system level (relevant system processes in the department, educational materials), (process indicators) at the practitioner level (nurses' knowledge, attitude, and knowledge about psychological distress), (outcome, indicators of the project): (structural indicators) at the system level (relevant system processes and educational materials in the department), (process indicators) at the practitioner level (nurses' knowledge, attitude and behavioural level related to psychological distress, and the rate of implementation of each review indicator), and at the patient level (the incidence and degree of psychological distress, improvement of the patients' psychological status, and the patients' quality of life). S (Setting, evidence application site): screening, assessment, response, referral, follow-up. E (Evidence Application Place): oncology wards and other related institutions. T (Type of Evidence): clinical decision-making, clinical practice guidelines, best practices, evidence summaries, systematic evaluations, expert consensus, randomised controlled trials, etc.

#### 2.1.2. Evidence Search

A top-down data search was conducted according to the "6S" evidence resource pyramid model. The search included BMJ Best Practice, UpToDate, Cochrane Library, JBI Centre for Evidence-Based Health Care, Guidelines International Network (GIN), Scottish Intercollegiate Guidelines Network (SIGN), National Comprehensive Cancer Network (NCCN), Registered Nurses Association of Ontario (RNAO), European Society of Medical Oncology (ES-MO), American Society of Clinical Oncology (ASCO), European Society of Oncology (ES-MO) and American Society of Clinical Oncology (ASCO), Italian Association of Medical Oncology (AIOM), Medline, Embase, SinoMed, CINAHL, PubMed, Web of Science, the official website of the National Health Commission of the People's Republic of China, China Knowledge Network (CKN), Wanfang Database (WFD), Wipo Database (WDB), and China Biomedical Literature Database for all evidence on the management of psychological distress in advanced cancer patients. Search terms in Chinese: advanced, terminal, end-stage; cancer; psychological distress, psychological crisis; management, care.

Search terms: advanced, end-of-life, terminal, near-death period, end stage; cancer, tumor, oncology, neoplasms; psychological distress, psychological crisis, psychological pain, mental pain; hospices, hospice care, palliative care, terminal care, disease management, management, nursing. The search period is from January 2010 to March 2024.

#### 2.1.3. Inclusion Criteria

Inclusion criteria: 1) the study object is to assess the psychological distress of pa-

tients with advanced cancers; 2) the content addresses the screening, assessment, response, referral and follow-up of psychological distress in patients with cancers; 3) the types are: guidelines, systematic evaluations, evidence summaries, high-quality randomized controlled trials, and expert consensus; and 4) the languages of the included literature are set to be Chinese and English. Exclusion criteria: 1) guideline interpretation type of literature; 2) duplicate publication or already have an updated version; 3) literature with incomplete information and full text unavailable; 4) graded C by literature quality assessment.

#### 2.1.4. Literature Quality Evaluation

Because the clinical decision-making source BMJ Best Practice, UpToDate, belongs to the top level of evidence in the "6S" pyramid, and the quality of the evidence is high, the evidence that is consistent with the present study and the clinical application scenario in China was directly adopted. The guidelines were evaluated by the Appraisal of Guidelines for Research and Evaluation II (AGREE II). Expert consensus, best practice, and randomised controlled trials were evaluated using the Australian JBI Centre for Evidence-Based Health Care's Authenticity Evaluation Tool for Opinion and Consensus Articles and the Authenticity Evaluation Tool for Randomised Controlled Trials, respectively. Summaries of evidence were evaluated using the Critical Appraisal for Summaries of Evidence (CASE). Systematic evaluations were evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR). In the end, we obtained 13 papers that met the inclusion criteria, including 3 guidelines, 1 best practice, 1 evidence summary, 4 systematic reviews, and 4 randomised controlled trials (see Table 1 for the quality assessment of the included guidelines).

Included in the literature	A particular year	Source	Туре	Title	Recommended level
Crawford <i>et al</i> . [5]	2021	ESMO	Finger post	Hospice care for adult cancer patients	В
Riba <i>et al</i> . [6]	2019	NCCN	Finger post	Distress Management, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology	А
NCCN [7]	2020	NCCN	Finger post	NCCN patient guidelines: psychological distress for patients during cancer care	В
Rodin <i>et al.</i> [8]	2020	ASCO	best practice	Psychological interventions in patients with advanced disease: an impact on oncology and palliative care	А
Yan <i>et al</i> . [9]	2012	JBI	Summary of evidence	Psychological distress thermometer used in patients with malignancy	А
Wang <i>et al.</i> [10]	2024	PubMed	systems assessment	Progress in the self-compassion in patients with malignancy	В
Xiao <i>et al</i> . [11]	2019	PubMed	systems assessment	The impact of dignity treatment on dignity, mental health, and quality of life in palliative care cancer patients	Α

**Table 1.** General information and quality assessment of the included literature (n = 13).

Continued					
Kang <i>et al</i> . [12]	2018	PubMed	systems assessment	Significance-centered interventions in patients with advanced or advanced cancer	A
Mitchell [13]	2010	PubMed	systems assessment	Brief screening tool for cancer-related distress	В
Lu <i>et al.</i> [14]	2022	PubMed	randomized controlled trial	Research on the hospice care needs of end-stage cancer patients is advanced	В
Li <i>et al</i> . [15]	2018	Know the net	randomized controlled trial	Progress in psychological interventions based on acceptance and commitment therapy in negative emotions in breast cancer patients	В
Serfaty <i>et al.</i> [16]	2011	Cochrane Library	randomized controlled trial	Study on the clinical effectiveness of aromatherapy massage and cognitive behavioral therapy for psychological distress in cancer/palliative care patients	В
Pan <i>et al.</i> [17]	2023	Know the net	randomized controlled trial	The application of hierarchical psychotherapy of psychological distress thermometer in patients with breast cancer radiotherapy and its influence on psychological pain, perceptual stress and coping style	А

2.1.5. Evidence Extraction Evaluation and Review Indicator Generation

17 pieces of evidence were initially extracted for training and assurance, screening, assessment, timing of intervention, non-pharmacological interventions, and health education through the JBI evidence-based framework [18] [19], structured search of the literature, and quality evaluation and integration; 4 pieces of evidence were deleted after the FAME evaluation, and 13 review indicators were constructed using structured observation, questionnaire, and interview methods, as see in Table 2.

Evidence category	Content of evidence	Evidence level	Recommended level	Review indicators	Review object	Review method
Training and guarantee	1. A multidisciplinary team should be established, including managers, doctors, nurses, psychotherapists, and psychiatrists [5]	4	A	1. The hospital has an interdisciplinary psychological care team	datum	View information
	2. Education and training programmes should be developed to ensure that health professionals have the knowledge and skills to assess and manage psychological distress [5]	5	Α	<ol> <li>The department has a psychological distress management system and process</li> <li>The pass rate of psychological distress assessment and management knowledge training and assessment was 100%</li> </ol>	paramedic	View information Questionnain and star assessment
Screen	3. All patients with advanced tumors should be screened with effective, reliable and objective tools, and provide corresponding services at	5	Α	4. All patients were assessed using psychological distress (DMSM)	patient	Check the medical records

Table 2. Table of indicators for the evaluation and review of the integration of evidence.

	screening to ensure follow-up diagnosis and treatment [6]					
Estimate	4. Pay attention to identify patients with high-risk of psychological distress, such as long-term treatment or hospitalization, mental disorders, suicide attempts, communication disorders, family/caregiver conflict, inadequate social support, history of depression, and cancer types associated with the risk of depression (e.g. pancreatic cancer, head and neck cancer) [7]	5	Α	5. Identify patients with a high risk of psychological distress	patient	Live questions/qu estionnaires
	5. When applying DT, in the overall evaluation of patients with advanced tumors, 4 points should be used as a cut-off value to judge the pain degree of patients [7]	4	A	6. Further assessment (anxiety/depression), triage/referral.	patient	View nursing records
	6. It is recommended to continuously and dynamically assess patient psychological distress, especially during changes in disease recurrence, progression, poor control of symptoms, and complications [7]	5	В	7. Responsible nurses evaluate regularly/dynamically according to the timing of assessment	patient	Live view
	7. Screening should determine the presence, extent, and nature of distress and target further evaluation [7]	5	A			View nursing records
Intervention timing	8. It is recommended that when the NCCN psychological distress thermometer scores 6 points, it is determined whether to be managed by an interdisciplinary psychological care team based on the clinical situation [9]	5	Α			View nursing records
gical	9. It is recommended to keep the ward quiet, with soft light, clean air, suitable temperature and humidity, so as to maximize the patient's sense of security and control [11]	5	В	8. Meet the environmental setting of the patient ward and keep the environment comfortable	scene	Live view
	10. It is recommended that the ward layout meet the preferences of patients and their family members as far as possible, allow patients to retain their own lifestyle, and promote the care and visit of patient's family and friends [11]	5	Α			View nursing records
	11. It is suggested to choose symptomatic psychological nursing methods according to the different types of psychological distress of patients [10]	5	Α	9. According to the different types of patients' psychological pain, the corresponding psychological care method is selected	nurse	View nursing records

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	12. For patients with mild psychological pain, the attending physicians and nursing staff will provide emotional support, psychological education and other routine treatment, encourage patients to maintain a correct lifestyle, and encourage patients to adjust their psychological state at the self-level [10]	4 s	Α		
	<ol> <li>For patients with moderate to severe psychological distress, joint professional psychological consultation management was conducted on the basis of mild psychological distress intervention [14]</li> </ol>	4	A		
	14. Clinical medical staff can use psycho educational interventions, music therapy, relaxation training, supportive group therapy, peer education, and physical exercise to help patients improve their mood [18]	5	A	10. Conduct group counseling patien for fellow patients once every two weeks	t View information
	<ol> <li>Comprehensive psychological interventions are recommended to provide patients and their families</li> <li>[16]</li> </ol>	5	A	11 The patient had follow-up datum records one week after discharge	n View information
Health education	16. It is suggested to promote the pre-established medical care plan. The communication tools such as heart-to-heart card games can be used to assist patients and their families in the communication and dialogue on patient preferences, disease treatment plans, prognosis arrangements, and target plans, and provide corresponding nursing support, which can significantly improve the psychological distress level of patients [16]	5b	Α	12. Patients with moderate and nurse severe psychological distress were given pre-established medical care programs	View information Interview patients
	17. Patients and their families are recommended to appropriately refer to the psychological distress education materials of cancer patients, such as NCCN, patient guidelines: patient psychological distress during cancer care, to help patients understand the causes of psychological pain, forms of expression, help, self-regulation methods, etc. [16]	5b	В	13. Monthly self-management datum of psychological distress publicity, patients and caregivers have 90% knowledge of the training content	n View information

## 2.2. Subjects of Practice

Convenience sampling was used to select the 12 nursing staff included and the 79 patients included in this ward from April-June 2024 with the same inclusion and exclusion criteria as the baseline review group. The 10 nursing staff included at the time of the baseline survey and the 74 patients included in this ward from July-September 2024 with the same inclusion and exclusion criteria of the baseline survey were the evidence application group evidence application group. Patient inclusion criteria: 1) Age 18 - 75 years old. 2) Advanced tumour patients. Exclusion criteria: 1) People with impairment of perception, understanding and expression. 2) Those who are delirious or have serious mental illness. 3) Those who are depressed or take other mental disorders. 4) Those who are on psychotropic drugs. 5) Those who have recently participated in psychological interventions related to psychological distress. Nurses' inclusion criteria: engaged in oncology nursing  $\geq$  1 year, and voluntarily participated in this study. Exclusion criteria: Further training, rotation nurses.

## 2.3. Evaluation Indicators

The implementation rate of the review indicators for the management of psychological distress in patients with advanced oncology, the level of nurses' knowledge, attitudes and behaviours related to psychological distress in patients with advanced oncology, and the incidence of moderate to severe psychological distress in patients with clinically advanced oncology.

## 2.4. Analysis of Influencing Factors

The project team analysed barriers and reasons in the clinical translation of evidence based on the evidence-based continuous quality improvement model according to the results of the status quo review by team members. Through focus group discussions, a fish bone diagram is drawn based on the 4M1E theory, and barrier factors are analysed facilitators and change strategies are constructed for each review indicator, see **Table 3**.

## 2.5. Statistical Processing

SPSS 21.0 statistical software was used to analyse the data. Measured data were statistically described by a kind of  $x \pm s$ , count data were statistically described by percentages, t-test and chi-square test were used for comparison between groups, and P < 0.05 was considered as statistically significant difference.

## 3. Results

## 3.1. General Information of the Study Population

153 patients were included in this study, including 79 cases in the baseline review group and 74 cases in the evidence application group, and the 2 groups of patients' gender, age, education level, and basic diagnosis, and the difference was not statistically significant (P > 0.05), see **Table 4**.

Table 3. Barriers analysing facilitators and constructing change strat	egies.

Review of the project	Disorder factors t	Promoting agent	Action strategy
Metric 1, 2, 12	<ol> <li>Nursing staff have weak knowledge of the definition, harm and prevention of tumor-related psychological distress</li> <li>Lack of psychological assessment tools for cancer patients</li> <li>Lack of whole-process management system and process of psychological distress of cancer patients.</li> <li>Qualification is required for psychological distress assessment</li> </ol>	<ol> <li>There is a psychological nursing plate in the tumor routine setting</li> <li>Hospital tumor routine care is in the revision</li> <li>There are 2 hospice care specialist nurses and 2 psychological counselors in our department</li> </ol>	<ol> <li>Determine the psychological distress assessment tool of cancer patients through literature review</li> <li>Improve the psychological distress management process and health education materials in the department</li> <li>Actively communicated with the department director and the nursing department, and established a multidisciplinary psychological care team</li> </ol>
Metric 3, 4, 5, 6	<ol> <li>Lack of knowledge and methods of assessing tumor-related psychological pain</li> <li>The department pays insufficient attention to psychological distress management</li> <li>Medical staff do not pay enough attention to cancer-related psychological distress intervention</li> </ol>	clinical practice of psychological distress has been retrieved 2. The standard hospital has carried out psychological distress management and medical insurance charges 3. In the establishment of	<ol> <li>Carry out knowledge training on tumor- related psychological distress in the department</li> <li>Carry out pre-established medical care plan training for medical staff</li> <li>Regular assessment of multi-form training level</li> <li>Establish specialized monitoring indicators for the incidence of tumor- related psychological pain.</li> </ol>
Metric 7, 8, 9	<ol> <li>The department is busy with working</li> <li>There are many types of tumor- related psychological pain, and the treatment is complex</li> <li>Increase the workload of nurses</li> </ol>	-	<ol> <li>Enter the psychological distress assessment scale into the information management system</li> <li>Carry out hierarchical intervention and implement referral/intervention according to the assessment results.</li> <li>Optimize the nursing workflow.</li> <li>Design a simple and clear mental health education manual</li> </ol>
Metric 10, 11, 13		in the health education 2. The follow-up shall be completed by the responsible leader, with professional	<ol> <li>Strengthen peer education, carry out and have group counseling</li> <li>Improve the discharge follow-up system, and increase the knowledge and guidance of home care for psychological pain</li> <li>Design a simple and clear health education manual</li> <li>Establish an effect evaluation mechanism</li> </ol>

# 3.2. Implementation of Review Indicators before and after the Clinical Translation of Evidence

The investigator ticked off whether the clinical practice was standardised in accordance with each review indicator through on-site review, on-site observation,

Group			Sex	М	arital stat	us	Deg	gree of educa	ation		Clinical diag	nosis
	Age (year)	Man	Woman	Unmarried	Married	Divorce or widowed	Junior high school and below	High school and technical secondary school	College degree or above	Lungs	Oesophagus	Mammary gland
Control group (79)	56.36 ± 4.85	35	44	8	36	16	15	33	12	13	38	9
Observation group (74)		39	35	9	32	19	12	38	10	15	32	13
t/F	0.759	0	.865		0.551			0.867			1.384	
Р	0.450	0.	6003		0.759			0.648			0.500	

**Table 4.** Comparison of baseline data between the two groups of patients  $(x \pm s, n)$ .

handover questions, and access to nursing records (the on-site review was blinded to the person being observed to avoid Hawthorne benefits). There were a total of 13 review indicators in this project, before the application of evidence, there was a gap between clinical practice and evidence, the baseline review had an implementation rate of 0% for 4 indicators, and the remaining 8 indicators had an implementation rate of 6.50% to 52.80%, none of which exceeded 60%, and after the application of evidence, 4 indicators had an implementation rate of 100.00%, and no indicator had an implementation rate of 0, and the implementation rate of the remaining indicators had an implementation rate of 65.20% to 88.60 percent.

#### 3.3. Incidence of Psychological Distress

The results of this study showed that the MSAS scores of all dimensions, DT scores, and PL scores of patients in both groups decreased after the application of evidence compared with the pre-intervention period, and the group with the application of evidence was lower than the group with the baseline review, and the incidence of moderate-to-severe psychological distress in patients with clinically advanced cancers was reduced from 76% to 43.5% (P = 0.04).

Nurses' knowledge, attitudes and behavioural levels related to psychological distress in patients with advanced cancers (nurses' knowledge, attitudes and behavioural levels related to psychological distress in patients with advanced cancers): a total of 14 nurses were included in this study, and due to the adjustment of the staff in the department, the application of the evidence was included in 12 of them, and 2 reviews were carried out before and after the application of the evidence, and the average age of the nurses was ( $26.48 \pm 7.47$ ) years old, with 1 male and 11 female, 7 with tertiary education and 12 with bachelor's degree. Through the introduction of evidence, nurses' knowledge, attitudes and behaviours in the management of psychological distress in patients with advanced oncology were improved, in which in the dimensions of knowledge and behaviour, the difference was statis-

#### tically significant (P < 0.05), see Table 5.

**Table 5.** Nurses' scores on the level of knowledge, attitudes and behaviours related to psychological distress in patients with advanced oncology before and after the application of evidence.

					Knowledge				
Group	п	Definition	Screen	Estimate	Reply	Referral with follow- up	Total points	Manner	Action
Baseline review	12	$1.30 \pm 0.53$	$12.48\pm0.91$	2.45 ± 1.35	$6.85\pm0.51$	17.79 ± 1.13	$40.88 \pm 2.87$	$4.45\pm0.62$	$3.76 \pm 0.61$
Application of evidence	10	1.73 ± 0.45	13.12 ± 1.34	6.21 ± 1.83	7.30 ± 0.64	21.27 ± 1.83	49.64 ± 3.93	$4.55\pm0.56$	4.30 ± 0.81
statistic		325.5	341.5	68.5	339.5	107	-10.342*	505.5	330.5
Р		0.001	0.006	< 0.001	0.002	< 0.001	< 0.001	0.569	0.003

#### 4. Discussion

#### 4.1. Impact of Evidence-Based Practice on Nursing Behaviour

This study shows that nurses' knowledge of psychological distress prevention and adherence to measures increased significantly, which is consistent with previous studies. This may be attributed to the multidisciplinary collaboration of standardised processes (e.g. the application of the psychological distress screening tool DT, the symptomatic management pathway) and hierarchical training mechanisms (e.g. communication skills training combined with scenario simulation). It is worth noting that nurses' perceptions of psychological distress shifted from "emotional problems" to "multidimensional symptom clusters", which led to a shift in the focus of nursing care from passive intervention to early prevention, a shift that is in line with the national hospice guidelines. This shift is in line with the concept of "whole-person care" advocated by the domestic hospice guidelines.

#### 4.2. Potential Mechanisms for Improved Patient Outcomes

The reduced incidence of moderate-to-severe psychological distress may be associated with the following mechanisms: 1) Prevalence of structured assessments: by incorporating the DT scale into routine nursing assessments, the identification of patients' psychological distress increased, ensuring that high-risk individuals received timely psychological interventions or referrals; 2) Integration of personalised interventions: evidence-based interventions (e.g. positive thought stress reduction, family meetings, pre-established healthcare plans) targeted to alleviate patients' concerns about the death anxiety, and family burden as core sources of distress [15]; 3) Enhanced nurse-patient trust: improved communication skills of nurses facilitated patients' willingness to express their emotions and avoided the insidious accumulation of distressing emotions.

This study constructed an evidence-based practice pathway for the management of psychological distress in patients with advanced cancers in line with China's cultural background [20], covering the closed-loop process of "screening-assessment-intervention-evaluation", which is highly operable in clinical practice. However, the study sample was limited to a single medical institution, and multi-centre validation is needed in the future.

#### **5.** Summary

This study integrated evidence-based recommendations for the management of psychological distress in patients with advanced oncology into clinical practice through an evidence translation strategy [21], confirming that the model is effective in enhancing nurses' professional competence, reducing the incidence of moderate-to-severe psychological distress in patients, and improving their quality of life. Further validation of the long-term effects of the intervention is needed in the future, exploring the use of digital tools (e.g. AI psychological screening) in dynamic assessment and focusing on the adaptation of the intervention model in the context of healthcare resource inequality. We advocate the inclusion of psychological distress management into the core indicators of quality of care for advanced oncology patients [22], and promote the standardisation and humanisation of hospice services.

## **Conflicts of Interest**

The authors declare no conflicts of interest regarding the publication of this paper.

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