Medical Faculty of Martin Luther University Halle-Wittenberg

Quality of Life Assessment in Breast Cancer Patients during Palliative Care Treatment in Indonesia

Results of a systematic review and a prospective cohort study

Dissertation
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Abstract

Palliative care (PC) can maintain the quality of life (QOL) of advanced cancer patients, but QOL research in PC settings in developing countries is limited. Therefore, this thesis aims to assess the QOL of advanced breast cancer patients during PC treatment in Indonesia.

This thesis is a cumulative doctoral project that consists of two studies. The first study was a systematic review that summarized potential factors influencing the QOL of advanced cancer patients in PC settings in developing countries. The second study examined the QOL and QOL domains of breast cancer patients.

To answer the thesis' aim, a systematic review using four electronic databases and a prospective cohort study were conducted. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the systematic review protocol registered in the Prospective Register of Systematic Reviews (PROSPERO). In the prospective cohort study, a total of 160 patients who met the study inclusion criteria: female, >18 years old, diagnosed with stage III or IV breast cancer prior to palliative oncology treatment, were recruited at the "Dharmais" Cancer Hospital in Jakarta, Indonesia between January and February 2020. Patients' socio-demographic and clinical characteristics were collected through interviews using a custom questionnaire. Patients' QOL was measured using the Indonesian version of the European Organization for Research and Treatment of Cancer QOL questionnaire (EORTC QLQ-C15-PAL).

The systematic review indicated around 30 factors (clinical or socio-demographic characteristics) associated with better or poor QOL of advanced cancer patients in 15 developing countries across regions and it was possible to implement PC in a limited-resource setting. Among other factors, age (> 65 years), marital status (married or ever married), education (high educational level), had additional care within PC, used complementary and alternative medicine, and practiced spirituality/religiosity were key components influencing QOL in advanced cancer in developing countries. The systematic review and baseline analysis of the cohort study also showed that QOL domains influenced QOL scores in advanced cancer patients. The cohort study demonstrated that emotional functioning and symptom scales (fatigue, pain, insomnia, and appetite loss) were associated with the QOL score. Therefore, if health care professionals focus on patients' specific QOL domains (emotional functioning, fatigue, pain, insomnia, and appetite loss) in this health facility, patients' QOL might be positively affected.

Gayatri, Dwi: Quality of life assessment in breast cancer patients during palliative care treatment in Indonesia: results of a systematic review and a prospective cohort study, Halle (Saale), Univ., Med. Fac., Diss., 76 Pages, 2022.

Referat

Palliativmedizin kann die Lebensqualität (LQ) von Krebspatienten im fortgeschrittenen Stadium erhalten, jedoch ist diese Forschung vor allem in Entwicklungsländern nur begrenzt vorangeschritten. Das Ziel dieser Arbeit ist es, die LQ von Brustkrebspatientinnen im fortgeschrittenen Stadium während der Palliativmedizin in Indonesien zu untersuchen.

Die vorliegende Arbeit ist eine kumulative Dissertation bestehend aus zwei Studien. Die erste Studie ist eine systematische Literaturrecherche, die potenzielle Faktoren zusammenfasst, die die LQ von Krebspatientinnen im fortgeschrittenen Stadium in der Palliativmedizin in Entwicklungsländern beeinflussen. Die zweite Studie untersucht die LQ und die Lebensqualitätsbereiche von Brustkrebspatientinnen in Indonesien.

Zur Beantwortung des Ziels der Arbeit wurden eine systematische Literaturrecherche in vier elektronischen Datenbanken sowie eine prospektive Kohortenstudie durchgeführt. Die systematische Literaturrecherche folgte den *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* und dem Protokoll der systematischen Literaturrecherche, dass im *Prospective Register of Systematic Reviews* registriert wurde. In der prospektiven Kohortenstudie wurden insgesamt 160 Patientinnen rekrutiert, die folgende Einschlusskriterien für die Studie erfüllten: weibliches Geschlecht, Alter über 18 Jahre, Brustkrebs Diagnose im Stadium III oder IV vor einer palliativ-onkologischen Behandlung und eine Behandlung im "Dharmais" Cancer Hospital in Jakarta, Indonesien zwischen Januar und Februar 2020. Die soziodemografischen und klinischen Merkmale der Patientinnen wurden durch Befragungen mit speziellen Fragebögen erhoben. Die LQ der Patienten wurde mit der indonesischen Version des *European Organization for Research and Treatment of Cancer* (EORTC QLQ-C15-PAL) gemessen.

Die systematische Literaturrecherche ergab rund 30 Faktoren, die mit einer besseren oder schlechteren LQ von Krebspatienten im fortgeschrittenen Stadium in 15 Entwicklungsländern in Verbindung gebracht wurden konnten. Neben anderen Faktoren waren Alter (> 65 Jahre), Familienstand (verheiratet oder jemals verheiratet), Bildung (hohes Bildungsniveau), zusätzliche Betreuung im Rahmen der Palliativmedizin, Nutzung von Komplementär- und Alternativmedizin und praktizierte Spiritualität/Religiosität, Schlüsselkomponenten, die die LQ von Krebspatienten im fortgeschrittenen Stadium in Entwicklungsländern beeinflussten. Die systematische Literaturrecherche und die Basisanalyse der Kohortenstudie zeigte, dass die LQ bei Krebspatienten im fortgeschrittenen Stadium durch die Lebensqualitätsbereiche beeinflusst wird. Die Bereiche emotionales Verhalten, Müdigkeit, Schmerzen, Schlaflosigkeit und Appetitlosigkeit mit dem Lebensqualitätswert assoziiert waren. Diese spezifischen Lebensqualitätsbereiche (emotionales Verhalten, Müdigkeit, Schmerzen, Schlaflosigkeit und Appetitlosigkeit) sollten zukünftig in Palliativemedizinische Einrichtungen in besonderer Form berücksichtigt und behandelt werden, um die LQ der Patientinnen nachhaltig zu verbessern.

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List of Abbreviations

CAM	Complementary and alternative medicine
CINAHL	Cumulative index to nursing and allied health literature
Embase	Excerpta medica database
EORTC	European organization for research and treatment of cancer
EORTC QLQ-C15-PAL	Validated quality of life questionnaire for advanced cancer stage
EORTC QLQ-C30	Validated quality of life core questionnaire for cancer patients
EQ-5D	European quality of life dimension
FACIT	Functional assessment of chronic illness therapy
FACT-G	Functional assessment of cancer therapy-general
GBCI	Global breast cancer initiative
GDP	Gross domestic product
HICs	High-income countries
LICs	Low-income countries
LMICs	Lower-middle-income countries
MEDLINE	Medical literature analysis and retrieval system online
NCDs	Non-communicable diseases
PC	Palliative care
PHC	Primary health care
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROs	Patient-reported outcomes
PROSPERO	Prospective register of systematic reviews
QOL	Quality of life
RCTs	Randomized control trials
SD	Standard deviation
SDGs	Sustainability development goals
SF-36	Short form 36 health survey questionnaire
UHC	Universal health coverage
UN	United nations
UNESCO	United nations educational, scientific, and cultural organization
WHO	World health organization
WHOQOL BREF	World health organization quality of life instrument

1. Introduction and Objectives

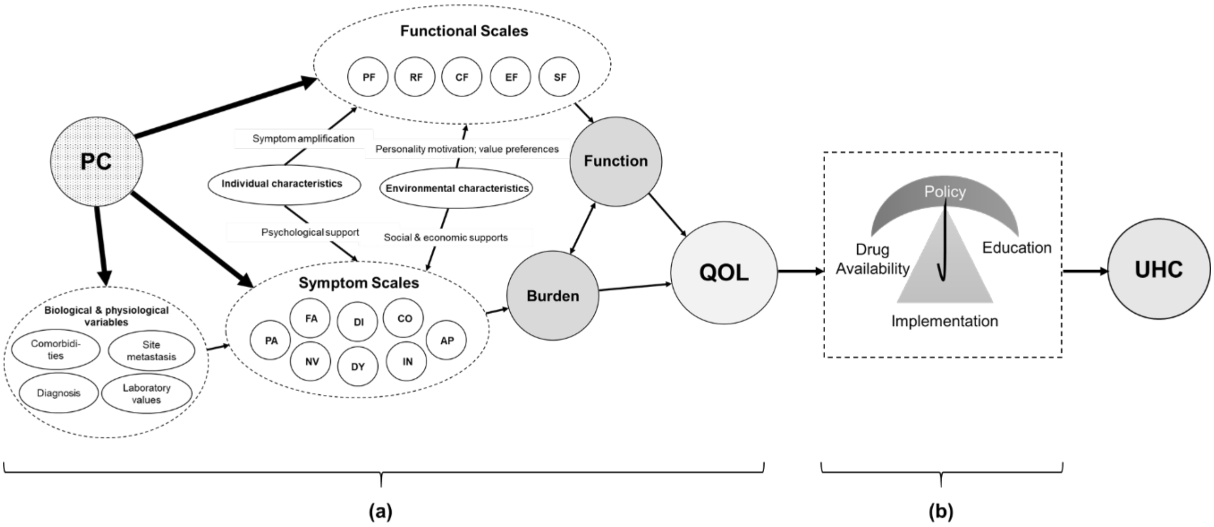
1.1. Disease burden of breast cancer

Breast cancer is a major public health problem across the globe. Approximately, 2.3 million women worldwide develop this disease, and breast cancer is the fifth leading cause of cancer mortality in women, with 685,000 deaths in 2020 (1). Indonesia, with a population of 273 million inhabitants follows a similar trend. For decades, breast cancer has contributed to the mortality and morbidity of Indonesian women with an annual incidence of 65,858 in 2020 (2). In 2040, it is expected that 3.2 million women will live with breast cancer, most of them from lower-middle-income countries (LMICs) (3). In these countries, the diagnosis for most cancers is frequently (70%) made at advanced stages when treatment options are limited and/or not accessible (4). Breast cancer patients often experience long-term chemotherapy or radiotherapy treatment and accumulation of psychological distress, chronic pain, and fatigue, which leads to worse overall quality of life (QOL) (5).

1.2. Palliative care

When no more curative options are available for cancer patients, the main goal of long-term care is to reduce symptoms' burden and maintain patients' QOL. Both goals are possible by referring the patient to the palliative care (PC) unit for management. PC was introduced in the 1990s and was defined by the World Health Organization (WHO) as "an interdisciplinary care approach that improves the QOL of patients with any serious illness and their families, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual (6)." PC is included in the 2015 United Nations (UN) Sustainable Development Goals (SDGs) target 3 together with promotion, prevention, treatment, and rehabilitation (7). Evidence showed that when combined with standard cancer care, PC provides better QOL, improves symptoms control, and better survival outcomes than standard care alone (8). The WHO also emphasizes that PC is given to cancer patients as early as possible during their cancer management regardless of their cancer stages or types to improve patients' QOL (9). Similarly, QOL framework models showed that PC could be implemented from the time of diagnosis and during treatment to achieve a better QOL (Figure 1a) (10-12). However, in most LMICs hospitals PC is provided only in the advanced stages of cancer progression (13).

PC is a fundamental component in breast cancer control programs. The WHO launched global breast cancer initiative (GBCI) to improve breast cancer outcomes and reduce breast cancer deaths by 2.5% per annum to save 2.5 million lives by 2040 (14). This strategy has the same objective as the SDGs to provide care for all and offers an approach to translate the successful lesson learned in high-income countries (HICs) to be adopted in LMICs. The GBCI consists of comprehensive cyclic three pillars corresponding to a breast cancer disease course and PC is included in this operational approach (14). The first pillar is health promotion and early diagnosis in patient's interval phase and aims to diagnose at least 60% of invasive breast cancer stage I or II. The second pillar focuses on timely breast diagnostics to diagnose within 60 days. PC is included and plays a key role in the third pillar (comprehensive breast cancer management) in the treatment interval phase. The third pillar aims to provide 80% undergo multimodality treatment without abandonment with a successful return to the community (14).



AP appetite loss; *CF* cognitive functioning; *CO* constipation; *DI* diarrhea; *DY* dyspnea; *EF* emotional functioning; *FA* fatigue; *IN* insomnia; *NV* nausea and vomiting; *PA* pain; *PC* palliative care; *PF* physical functioning; *QOL* quality of life; *RF* role functioning; *SF* social functioning; *UHC* universal health coverage

Figure 1. The framework of patient outcome in health-related quality of life conceptual model (a) and the WHO Public Health Strategy for palliative care development (b) (used with permission and modified from (10-12, 15))

The need for PC is rapidly increasing due to the aging population, cancer, and other non-communicable diseases (NCDs). It is estimated that the need for PC at the end of life is expected to double in 2060 (16). NCDs will contribute almost 69% of this need. Individuals with cancer, human immunodeficiency virus/acquired immunodeficiency syndrome, cerebrovascular, dementia, and lung diseases are the most common group needing PC services (16). While the right of chronically/life-threatening ill individuals to be free of avoidable disease-related symptoms has been recognized and PC has been declared a universal human right (17), its accessibility is limited or unavailable for millions in need, especially in patients from LMICs (16, 18). PC inequities also exist within HICs, for example, where a particular population segment might have less access to PC due to marginalized or gradient socio-economic status (19-21).

The global PC development follows the WHO Public Health Strategy (Figure 1b), aiming to increase access to PC services by integrating them into a country's main health care systems (15). For achieving PC for all, including PC in a country's Universal Health Coverage (UHC) strategy is highly recommended by several international agencies, such as the WHO and the World Palliative Care Alliances (6). Unfortunately, outside of the western developed countries, PC is often underdeveloped and access to quality PC continues to be limited. According to the WHO, PC services are more widely available to patients in HICs (81% for home- or community-based; 70% for primary health care/PHC) compared to upper-middle-income countries (37%; 38%), LMICs (15%; 13%), and low income countries (LICs) (10%; 19%) (22). The main differences among these countries are explained by the updated levels of PC development that are categorized into four criteria (18). PC services with an adequate level of integration to mainstream health care (category 4b) reportedly existed only in 30 (15%) countries that mostly pose a higher economic development (18). These countries which represent 14.2% of the world population have provided an adequate specialized PC and ensured UHC to their citizen. In contrast, most LMICs (65 countries), including Indonesia, with 47.7% of the world population only had isolated PC provision (category 3a). This PC development category is described as patchy in scope and not well supported, considering that the sources of funding are often heavily donor-dependent, there is limited drugs availability, and PC services are limited to address the needs of the total population (18). In the current global inequity of PC, 80% of deaths with serious health-related suffering occurred in LMICs where the vast majority cannot access the most basic symptoms management or pain relief (23). Despite international initiatives on the urgency of PC implementation and evidence of PC benefit, wide disparities in PC development exist across countries and within countries.

Palliative care in Indonesia

Indonesia is the largest archipelago in the world with around 17,504 islands and for decades, its geographical aspects remain a major challenge in achieving equal health distribution. Administratively, Indonesia consists of 34 provinces, 514 districts, and 7,230 sub-districts (24). Indonesia's health care system follows a provider-based model that consists of primary, secondary, and tertiary levels (25). The PHC is provided by *Pusat Kesehatan Masyarakat* (health center), which aims to provide equal health access to communities and focuses on health prevention and promotion. While PHC is commonly found in sub-districts, secondary and tertiary health care is located in districts or provinces. The secondary and tertiary health care level provides curative and rehabilitative methods. Four types of hospitals (A, B, C, and D) mainly differ in resources and capacities are offered by secondary and tertiary health care (24). While hospital types A and B are tertiary health care providers, hospital types C and D function as secondary health care providers. Oncology units that offer cancer care services can be found in type A and B hospitals. According to the 2020 Indonesia Health Profile (24), the national ratio of a health center and sub-district has achieved the government target to provide one health center in each sub-district (as an indicator of public access to PHC). Similarly, the ratio of beds per 1,000 inhabitants has achieved the WHO recommendation; however, the health status and quality, availability and capacity of health services vary (24). In 2004, a major financial reform of health services occurred as a government commitment to achieving SDGs. The National Social Security Law (*Sistem Jaminan Sosial Nasional*) has initiated a comprehensive social security framework that includes a strategy for UHC. Conceptually, this framework aims to ensure the financial protection of Indonesian citizens in equal access to health care services (26).

PC development in Indonesia has been slow compared to neighboring countries, i.e., Singapore or Thailand (26). PC implementation was established in some Indonesian hospitals because the Minister of Health Decree related to the WHO PC initiative began in the 1990s (26). However, studies showed that Indonesia's PC services were not fully integrated into mainstream health care services (18), varied across provinces (27), and were stagnant in isolated PC provision level (category 3a) for nearly three decades (18, 26). PC services are currently only available in a few Indonesian major cities where most health care facilities for cancer treatment are located. However, as a UN member state, Indonesia has committed to accomplishing the SDG target 3 by integrating PC into the National Cancer Control Program since 2014 (27). In 2016, the Indonesian government made an effort to revitalize the PC implementation in several hospitals, such as the "Dharmais" Cancer Hospital and Cipto Mangunkusumo Hospital in Jakarta, Sutomo Hospital in Surabaya, Wahidin Sudirohusodo in Makasar, and Sanglah Hospital in Denpasar. Consequently, a PC unit was reestablished in those hospitals that provide cancer patients with several services mainly focused on pain management (28). Before 2016, palliative treatment was provided through oncology units across Indonesian hospitals (type A and B). The main palliative oncology treatments were chemotherapy and hormonal therapy, while radiotherapy and surgery were used if required to reduce symptoms, but not for curative purposes (28).

1.3. Quality of life

Since the 1970s, the concept of QOL has been increasingly used in research and clinical practice. QOL emerged as an important parameter for evaluating the quality and outcome of health care (29) and was also commonly used in randomized control trials (RCTs) over the past decades (30). There are two possible explanations for the increasing interest in QOL in health science. Firstly, an increased life expectancy is owing to improved medical therapies. Consequently, many individuals are diagnosed with chronic diseases than with terminal illnesses. Therefore, QOL should be used to assess health outcomes with mortality and morbidity (31). Secondly, due to advancements in medical and surgical technologies. As available treatments increase, thorough consideration of the benefit-burden ratio of equivalent therapies is highly needed (32). Therefore, QOL measures are recommended when assessing the benefits of various treatment options.

QOL is considered a self-reported assessment or patient-reported outcomes (PROs) and an important tool in research and clinical settings (11). The QOL concept can be defined as how a patient's usual or expected physical, emotional, and social well-being are affected by a medical condition and its treatment (33). This multidimensional and multidisciplinary concept affects the whole human aspect, e.g., psychosocial, spiritual, financial, and physical (12, 34). It provides a more accurate evaluation of the well-being of patients and the benefits and/or side effects that may result from the medical intervention or disease treatment. Despite its subjective aspect, QOL is considered valid, reliable, and responsive to capturing important clinical changes (11, 34). QOL is also an indicator of the disease's impact on a patient, helpful in the empowerment of patients and treatment decision-making (35). Assessing QOL is considered adequate for a patient-centered approach in the UHC framework. Therefore, QOL is an important PRO that provides insight into disease burden and is a key element of health care evaluation.

Quality of life measures

Various QOL instruments exist and were developed by several organizations, i.e., the WHO with its WHOQOL BREF, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group has constructed the EORTC QLQ-C30 core questionnaire, and the Functional Assessment of Chronic Illness Therapy (FACIT) Group has created the Functional Assessment of Cancer Therapy-General (FACT-G) instrument (Table 1). For example, Albers et al. identified 29 different QOL instruments in their systematic review with various measurements aim, content, target population, method, completion time, and clinic metric quality (36). However, a primary difference across QOL instruments is whether they are generic or specific QOL (34).

Generic QOL instruments are designed to be applicable across all diseases or conditions, different medical interventions, and populations (34). Some were initially developed with a population studies approach (the WHOQOL BREF) (37), even though later applied in clinical trial settings (34, 37). Generic QOL instruments are suggestively called "measures of health status" because they focus on physical symptoms and assume that poorer health indicates poorer QOL. Many of the earlier QOL questionnaires adopt this approach, i.e., the Sickness Impact Profile and the Nottingham Health Profile (34). Newer generic instruments strongly emphasize the subjective non-physical aspects and commonly include one or more questions about overall QOL (the Short Form 36 Health Survey Questionnaire/SF-36) (38). Moreover, some are appropriate for use with cost-utility analysis (the European Quality of Life Five Dimension/EQ-5D) (39) and allow patients to choose QOL aspects to their preferences (the Schedule of Individual Quality of Life) (34, 40). Generic instruments have the advantage that patients with various diseases may be compared against each other and the general population. However, they often fail to focus on particular concerns of patients with the disease and lack of sensitivity to detect differences owing to treatment policies comparison in clinical trials (34). Therefore, specific QOL questionnaires are developed and designed to be relevant to a particular condition or state, such as a disease-specific questionnaire for cancer (34). Despite focusing on a similar disease, there is substantial variation in content and wording among cancer-specific instruments, i.e., the EORTC QLQ-C30 and FACT-G. These instruments, which may be adequate for treatment comparison in clinical trials, aim to measure general QOL and include at least one general question about overall QOL or health. Despite the main difference, most QOL instruments have similarities in capturing the multidimensional (emotional, psychological, and physical) aspects of patients' health (41).

Several systematic reviews consistently showed that the EORTC QLQ-C30 and the FACIT are the most common QOL instruments used in health research (30, 42). A current systematic review pointed out that EORTC (40.7%) and FACIT (26.6%) QOL questionnaires were more popular compared to EQ-5D, SF-36, and the M. D. Anderson Symptom Inventory (7.6%, 5.4%, and 1.9%, respectively) across 646 cancer RCTs in published studies between 2004 and 2018 (30). The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea and vomiting), and global health and quality of life scale (Table 1) (43). It has been translated and validated into 110 languages and used in more than 3,000 studies worldwide (44). The core QOL questionnaire can be supplemented with disease-specific modules, and there is also a shortened version, which is suitable for research in PC or advanced cancer stages that consists of 15 items (EORTC QLQ-C15-PAL) (45). The FACT-G is a 27-item compilation of general questions divided into four primary health-related QOL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being (Table 1) (46). This questionnaire has been validated not only for cancer but also in a range of chronic diseases and has been translated and validated into more than 50 languages (47). A shortened version of a rapid symptom/concern scale consists of seven items and another version for assessing QOL in PC patients consists of 14 items. Both EORTC and FACT-G have item libraries with supplementary items on specific health issues to allow a more flexible assessment approach. The item libraries' flexibility may be particularly beneficial when evaluating new treatment types with toxicity profiles that differ from conventional treatments (34). The WHOQOL BREF is a generic QOL questionnaire developed to provide a short version of WHOQOL-100. It contains 26 questions and two overall QOL and general health assessment items (Table 1). This QOL questionnaire is developed to be applicable cross-culturally (37).

Table 1. Characteristics of EORTC QLQ-C30, FACT-G, and WHOQOL BREF

Characteristics	**EORTC QLQ-C30**	**FACT-G**	**WHOQOL BREF**
Developer	EORTC QOL Group	FACIT.org	WHO
Number of items	30	27	26
Response scale	Likert scale (4 or 7 points)	Likert scale (5 points)	Likert scale (5 points)
Recall period	Past week	Past 7 days	Past 4 weeks
Item format	Questions	Statements	Questions
Language availability	110	53	29
Required time for completion (minute)	11	5 to 10	10 to 15
Administration	Self-reporting, interview, computer	Self-reporting, interview, computer	Self-reporting
Scaling	Overall global health status	Overall FACT-G score (total of all items)	• Overall perception of health • Overall perception of QOL
	5 functional scales: • Physical functioning (5 items) • Role functioning (2 items) • Emotional functioning (4 items) • Cognitive functioning (2 items) • Social functioning (2 items) Symptom scale: • Fatigue (3 items) • Pain (2 items) • Nausea and vomiting (2 items) • 6 single-item symptoms: dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties	4 well-being subscales: • Physical well-being (7 items) • Social/family well-being (7 items) • Emotional well-being (6 items) • Functional well-being (7 items)	Domain 1: physical health (7 items) Domain 2: psychological (6 items) Domain 3: relationships (3 items) Domain 4: environment (8 items)

EORTC QLQ-C30 the European Organization for the Research and Treatment of Cancer quality of life questionnaire core (44); *FACIT* Functional Assessment of Chronic Illness Therapy; *FACT-G* Functional Assessment of Cancer Therapy-General (47); *WHOQOL BREF* World Health Organization quality of life instrument (37).

Factors influencing the quality of life in patients with advanced cancer

Various factors influence the QOL of cancer patients. According to Wilson and Cleary, medical and non-medical factors might be associated with QOL (Figure 1a) (12). The medical aspects are biological and physiological factors, symptom status, and functional status. The non-medical aspects are socio-demographic characteristics, i.e., age, gender, socio-economic status, and social and family supports (10, 12). The framework model shows three key components affecting QOL (Figure 1a). The first component is biological and physiological variables, e.g., diagnosis, laboratory values, a measure of physiological function, and physical examination findings which often manifest in health (12). Biological and physiological variables are theoretically reflected by changes in cell, organ, or organ system functions. Abnormality changes in the first component affect symptoms scales (the second component) (11), which often cause functional disorders (the third component) (11, 12). As cancer patients' QOL is affected through all disease courses, maintaining patients' QOL is possible if PC strategy can be implemented in each component regardless of cancer types or stages.

For patients with breast cancer, the QOL aspects are dominated by how symptoms, e.g., pain, fatigue, or nausea, are managed or controlled (Figure 1a). For high-quality oncology PC in advanced cancer patients, it is essential to monitor QOL in clinical practice in a suitable manner (34, 36). The assessment of QOL in patients under PC is an important process for identifying the patient's overall condition and evaluating the services provided to the patient. It increases awareness among health care professionals to better anticipate patients' changing needs and improves clinical outcomes (fewer emergency room visits, fewer hospitalizations, and a longer duration of palliative chemotherapy) (34). It is also associated with improvements in patient outcomes during consultations and patient satisfaction in clinical settings (48). The best method to monitor QOL in patients is to ask patients themselves, as asking health professionals or relatives is considered a less accurate method for estimating a patient's QOL.

1.4. Barriers/issues and objectives

Despite growing evidence of PC's positive impact on advanced cancer patients' QOL, several barriers/issues remain a serious challenge that might prevent PC implementation. The PC development model (Figure 1b) developed by the WHO requires four important pillars: policy, education, medication availability, and implementation (15). The policy is the fundamental pillar that reflects a government commitment and without it, other pillars are less likely to be introduced. Among different policy components, laws/regulations that acknowledge and define PC as part of the health care system and a national plan on PC implementation are considered two key components (15). However, a current review assessing the global status of PC policy development found that only 55 (27%) countries worldwide have any national strategy for PC and are mostly concentrated in western countries (49). In addition, lack of educational programs and research on PC, lack of essential medications and organizational programs to deliver PC commonly exist as significant barriers, particularly in LMICs (22). Despite increasing research in this field (42), studies on QOL in PC are often unavailable in LMICs or mostly conducted in HICs (50, 51). Moreover, adopting or translating QOL research findings/recommendations from HICs into LMICs is challenging because of the different needs and socio-demographic/cultural characteristics between HICs and LMICs (35). It is also evident that QOL varies between and within countries (52, 53); therefore, whether QOL among cancer patients in LMICs is poorer or better than HICs is inconclusive. Moreover, a better understanding of QOL in breast cancer patients and its determinant factors in PC is necessary and can be beneficial for patients and health care providers to plan patients' cancer management. Therefore, this thesis aims to assess the QOL of breast cancer patients during PC treatment in Indonesia. In order to answer the thesis' aim, a systematic review was conducted to provide an initial perspective on factors affecting QOL in PC patients in developing countries and followed by conducting a prospective cohort study of advanced breast cancer patients at the "Dharmais" Cancer Hospital in Indonesia. However, in this thesis, only the baseline data of the prospective cohort study will be presented. The following research questions are assessed:

1. What are the individual characteristics of breast cancer patients during palliative oncology treatment in Indonesia?
2. What is the QOL score for breast cancer patients during palliative oncology treatment in Indonesia?
3. What factors influence the QOL score of breast cancer patients during palliative oncology treatment in Indonesia?

2. Discussion

This doctoral thesis assesses the QOL of advanced breast cancer patients from an Indonesian PC perspective. This dissertation is based on the publications that have addressed the research questions (Introduction 1.4). The first publication is a systematic review using four electronic databases (MEDLINE, Embase, CINAHL, and Web of Science) and aiming to summarize evidence from published literature on factors influencing cancer patients' QOL in PC units in developing countries. The systematic review followed a standard systematic review protocol of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered our systematic review with PROSPERO (CDR42019142567). We used search terms: 'quality of life', 'cancer', 'palliative care', and names of all developing countries (54) for articles published in English between January 1990 and February 2019. Our systematic review showed that several socio-demographic characteristics (older patients > 65 years, married/ever married, and high educational level) and cultural perspectives (used complementary and alternative medicine/CAM and practiced spiritual/religious activities) were key factors influencing QOL/QOL domains scores in PC in developing countries.

The second publication is the baseline analysis of the prospective cohort study. The study aimed to assess QOL in advanced breast cancer patients prior to palliative oncology treatment (at baseline) and identify which QOL domains influence the outcome of interest at the "Dharmais" Cancer Hospital in Indonesia. Patients at the oncology unit were invited to participate between January and February 2020. Before starting the interview, all participants provided written informed consent that was in line with the Declaration of Helsinki. The Indonesian version of the EORTC QLQ-C15-PAL was used to collect the QOL variables and was self-reported by patients (55). The study protocol was approved by the Ethics Committee of the "Dharmais" Cancer Hospital (136/KEPK/VII/2019) and acknowledged by the Ethics Committee of Medical Faculty of Martin Luther University Halle-Wittenberg (Processing No: 2021-139). The baseline data showed a high QOL score in advanced breast cancer patients before palliative oncology treatment. Some QOL domains (emotional functioning, fatigue, pain, insomnia, and appetite loss) were associated with QOL scores. Therefore, in this chapter, the main findings are further discussed in the state of research and linked to the direction of PC development strategy to achieve SDGs 2030 in Indonesia.

2.1. Study main findings in relation to the state of research: quality of life assessment and palliative care in cancer patients

Our studies support previous studies (56, 57) and conceptual frameworks (11, 12) that showed several factors, e.g., individual and environmental characteristics and QOL domains (functional and symptom scales) influence advanced cancer patients' QOL. Despite a few available QOL studies in LMICs, a comparison to previous studies with similar contexts needs to be discussed.

Only one Indonesian study in a similar context was found (58). The study showed a lower score for QOL, physical and emotional functioning (at 63 or below) and a higher score for symptom scales (> 25) at baseline compared to our study (59). This discrepancy might be due to the methodological aspects, such as the differences in study inclusion criteria. Despite using the similar EORTC QOL questionnaire, Kristanti et al. focused on all types of cancer, included men and women in their study, recruited patients who were aware of their diagnosis, and excluded patients who had a good functional ability (Palliative Performance Scale > 70) (58). However, Kristanti et al. also pointed out that emotional functioning influenced QOL score which was similar to our baseline analysis results (59). Similarly, studies (5, 60) and reviews (42, 61) in advanced cancer patients concluded that fatigue, insomnia, depression, pain, poor appetite, and functional scales (physical/emotional functioning) were the common symptoms experienced by these patients' group. Being diagnosed of having breast cancer can be detrimental for most women. This shocking news and side effect of medications and other aspects of illness might result in a traumatic life experience (62). Evidence showed that a traumatic life experience, such as cancer often causes low self-esteem, anxiety and depression (63, 64). In most cases, cancer patients who had depression experienced more sleep disturbance (insomnia) compared to non-depressive cancer patients (63, 65). Moreover, insomnia is closely associated with other cancer-specific symptoms, such as fatigue and pain and negatively affects physical and emotional aspects (61, 66). For example, pain would serve as a counter-stimulus and significant discomfort might keep patients from falling asleep (67). Consequently, these circumstances often manifest in a lack of coping ability and worst QOL (68). Symptoms relief management in PC for advanced cancer patients can result in better function and QOL. Evidence demonstrated that PC through psycho-education support (42), home PC (8, 69), social relationships (42), and oncology outpatient PC (70) showed positive effects on QOL, symptom burden, and survival. Therefore, identifying and addressing these symptoms through QOL assessment during PC or palliative oncology treatment by health care providers are important.

Among socio-demographic factors, cultural aspects seemed to be a key component affecting QOL in this context (21, 42, 71, 72). Similarly, our systematic review showed that cultural aspects (religiosity/spirituality and seeking alternative non-medical treatment) in advanced cancer patients in PC positively affected their QOL (73). The main possible explanation is that culture shapes every aspect of human life, including preferences about the disease and its treatment process (71, 72, 74). Patients' preferences are fundamentally influenced by availability, accessibility, and knowledge about disease treatment options (75). For patients with serious illness, their preference affects both processes and outcomes of care (75). For instance, in some cultures, the family often discusses and/or decides on treatment plans for an unhealthy family member, while others do not interfere with patients' decisions. In another cultures, the care decisions of the elderly are left to the children. Many countries, such as Indonesia, consist of different ethnic groups, religions, and cultural backgrounds; therefore, the health care practitioner should understand and recognize the various influences within and between patient groups that influence patients' preferences (71, 72). Assessing QOL can be used to accurately gain patients' personal experiences (71, 72), followed by a discussion on the results of QOL assessment (76, 77). Consequently, patient-provider communication is established and further individualized disease treatment is planned.

Cultural variation shows that fundamental human concepts vary, e.g., the meaning of life, suffering, and QOL. In advanced cancer patients, recognizing their cultural interpretations requires additional understanding and efforts from health professionals to accompany patients and their families with respect (72). For example, it is considered inappropriate and culturally insensitive to discuss impending death in many cultures. Therefore, health care providers should consider the beliefs of the family and patients before approaching individuals with poor prognoses. While religion and spirituality highly influence patients' health care decisions (71, 75), many health professionals may not consider this factor in evaluating and treating symptoms burden and PC. Lack of understanding of patients and families' beliefs can potentially damage the patient-provider relationship. Consequently, this lack of trust can be a barrier to appropriate cancer management, particularly in PC (72, 76). In an ethnically and culturally diverse society, health care providers need to respect and consider the cultural background of their patients.

Understanding patients' cultures can increase health professionals' knowledge to effectively manage patients' treatment and help the family adjust to the disease treatment process (72). Moreover, it is crucial for the health practitioner to feel comfortable asking patients about their disease management and care preferences. Therefore, providing health care professionals in PC with adequate communication skills through training is necessary.

2.2. Study implication: quality of life assessment and Sustainable Development Goals 2030 (Universal Health Coverage)

The 2030 Agenda for Sustainable Development, including 17 SDGs was launched at the UN Sustainable Development Summit in 2015 (7). Health is part of the SDG target 3 with objectives to "ensure healthy lives and promote well-being for all ages." Achieving UHC is one of the SDG targets 3 and aims that every individual has equal access to health services without financial hardship (7). These health services include prevention, treatment, rehabilitation, and PC. A patient-centered care approach is needed and recommended to accomplish UHC/SDG target 3; therefore, we need quality implementation of PC to achieve the target.

Ensuring PC for all can be delivered by following the WHO Public Health Strategy (Figure 1b). In this model, the key component is policy and is an umbrella term that covers the other three pillars (15). A good policy should be founded on evidence-based research, as research can effectively communicate the importance of health-related events to policymakers (49). The lack of evidence limits leverage and discussion with the policymakers to adequately allocate resources for PC services. The PC benefits have been acknowledged over the past decades (78-80), but the lack of research in this context exists across nations, particularly in LMICs (50, 51). Similarly, our systematic review found limited research (only 55 studies from 15 countries) in PC settings conducted to assess QOL of advanced cancer patients in developing countries (73). Two possible reasons can explain this discrepancy. The first reason is a country's policy perspective that often reflects its national budget allocation for research. For example, national allocation expenditure on research and development is closely correlated with the UHC service coverage within a country (18). The UNESCO reported that Germany allocated 3.1% of gross domestic product (GDP) to research and had a better score of 83 in UHC coverage (a score toward 100 describes an excellent UHC coverage) compared to Indonesia, which spent only 0.2% of GDP with a score of 57 (18). Similarly, the WHO stated that more countries in HICs (91%) allocated funds for PC services than in LICs (48%) (49, 81). The second reason is that research focus priority in oncology vastly outweighs the interest in PC development. For instance, the National Cancer Research Institute reported that only 0.3% of total cancer research funds from 2015 to 2016 in the United Kingdom were allocated to PC or hospice care (82). In contrast, cancer biology and treatment research received 28% and 36% fund allocation, respectively (82). Similarly, a small proportion of research spending in cancer allocated for PC topics occurred in the United States of America and Australia (83) which might further drive oncologists towards disease-directed treatment and focusing on curative treatments over improving QOL and PC. Narrowing this research gap among countries can be accomplished by two key strategies. The first is improving PC research strategies by identifying research priorities based on regional, cultural, and socio-economic contexts (37). The second is identifying resources to support PC research and promoting PC benefits for different stakeholders, such as patients, health care providers, and policymakers (84). From patients' perspectives, routine QOL assessment provides advantages, i.e., a better understanding of their function or burden of disease and addressing their symptoms to health professionals. Patients can discuss their expectations towards available treatment that meets their values and preferences (85). Consequently, health professionals can plan further treatment by considering patients' expectations. Unnecessary curative intent can be minimized and lowering health care allocation to other aspects is a sign of high-quality care. Therefore, the advantages of PC can provide stakeholders with motivation and encouragement to implement PC with QOL assessment as a key component on the road to UHC/SDGs by 2030 regardless of the limited-resource settings.

As stated in the Introduction, PC aims to maintain the QOL of patients with a life-threatening illness and implies a patient-centered approach (86). This approach focuses on patients in health care, while conventional care often focuses on the diseases and seems not to involve patients in the treatment plan (87). For example, in regular consultations, many symptoms are not identified or addressed for some reasons, e.g., patients perceive the symptoms burden (anxiety and depression) are irrelevant to their cancer care and often patients' QOL and symptoms are assessed by observers (88). While patients are the best source for reporting QOL, other observers, e.g., health professionals or caregivers may overestimate or underestimate patients' conditions (34). However, proxy assessment by a relative or other close observers is allowed if a patient cannot make a coherent response, e.g., patients are too young, too old, severely ill, or have a mental impairment (34). Frequent QOL assessment makes health professionals aware of their patient's symptoms (89). As relieving burdensome symptoms through a systematic QOL assessment is a core task within the patient-centered approach, the most important obligation of health care providers is to frequently use QOL assessment, discuss the results with patients, explain potential treatment, and make patients an active partner in the decision-making process. Understanding symptoms from patients' perspectives and experiences is essential in cancer diagnosis and treatment/care. Studies emphasized that assessing QOL in PC plays a key role in PC development/implementation in LMICs (90, 91). However, QOL assessment is often not regularly used in clinical settings (50, 51, 92), even though it is commonly used and shows advantages in clinical trials (93). Insufficient and unsystematic assessment of QOL is a major factor explaining inadequate symptoms relief in patients with cancer. Therefore, assessing QOL is a relatively simple activity that can be implemented daily in health care facilities regardless of PC or palliative oncology settings (94), and its findings can inform evidence-based and contextually relevant clinical practice.

The best strategy for palliative care integration models

In general, PC development in most LMICs was reported inadequate in all four pillars (18, 49). However, some countries, such as Indonesia have committed to supporting the international movement in implementing PC for all (18). This commitment is manifested by PC development strategy in their national health care agendas, but they have continuously faced difficulties along the process (18, 22). As achieving the gold standard PC development (category 4b) requires massive resources and time that are limited in most LMICs, UHC/SDG target 3 by 2030 across these countries might result in less achievement. Therefore, providing several potential approaches that can be effectively adopted across nations is necessary.

While PC integration has positive aspects for patients and their families and health care providers, there should be a way for most countries, particularly in poor-resource settings to adopt and implement it. Internationally, several different organizational models have been developed and tested in clinical studies that were again mainly conducted in HICs (95, 96). However, these models vary considerably in content, structure, and professional competence (87). The conceptual models of PC integration can be classified into time-based (advanced stage versus the entire disease course), provider-based (primary, secondary, and tertiary level), and setting-based (hospital versus community/home) models (95, 97). While these models identify important factors concerning the organization, professional competence, and timing as a part of the care pathway, no available models specifically describe the mechanism of patients' movement and communication process across primary and specialized levels of care or care settings. Therefore, The Lancet Oncology Commission proposes an empirical model that focuses on a provider-based conceptual model of primary, secondary, and tertiary PC provision delivered by generalists, oncology teams, and specialized PC teams (87). This model emphasizes the need for oncology and PC to fully integrate all settings and levels.

Primary PC sets as the basis of a pyramid in the Lancet Oncology Commission model and functions as the core skills and competencies, e.g., basic QOL assessment, adequate communication, and appropriate referral to available community-based supports (87, 98). It is best provided in the community, both in outpatient and home settings by general practitioners. Home-based PC plays a key component in this context, while it prevents unnecessary visits to the emergency unit/hospital admission and enables death at home (99). Secondary PC is mainly hospital-based and provided by the oncology teams in the specialist health care system, both inpatients and outpatients. Actors in this level, i.e., specialists in medical and surgical oncology, social workers, and psychologists should have core clinical competencies in PC, e.g., routine QOL assessment at least monthly and develop good communication on prognosis to a patient and primary care provider. Patients with complex or uncontrolled symptoms should be referred to available tertiary PC services (100). Tertiary PC is provided by physicians and other multidisciplinary teams with specialist PC training. Ensuring the care transitions among these three levels of care is important and a consensus was recommended by international PC experts using two criteria of needs-based and time-based as a guideline when detailed standardized clinical pathways are developed in oncology (87). Creating a strong, collaborative relationship between levels requires strategies, such as mentorship and advisory programs to facilitate access to tertiary care teams. This program includes out-of-hours support; involving primary PC providers in discharge planning discussions or family meetings for shared patients before home discharge; and maintaining good communication between community-based and hospital-based teams through shared electronic records (101). Consequently, this collaboration can improve family or general practitioners' confidence in providing primary PC and recognizing transitions in care (101).

As finding an appropriate PC model for most countries to achieve PC for all/UHC is important, PC needs to be integrated into national health strategy (15) and part of cancer control programs as emphasized by the GBCI (14). The lack of one or multiple pillars in the WHO Public Health Strategy for PC development remains a challenge in this circumstance. In most countries, the nature of cancer care systems is historically fragmented, cancer care services are accessible in limited health facilities, an inadequate number of specialization competencies, and lack of education on oncology during palliative medicine specialization or vice-a-versa (16, 87). Moreover, in most national cancer care, PC is not integrated with oncology and is often only an add-on to the disease-focused approach. Lack of willingness and capability to implement and prioritize PC in cancer plans, care programs, and clinical care pathways exists. Therefore, WHO recommends integrating PC implementation for a country to adjust the motivation by considering its culture and available resources (37).

Considering the Lancet Oncology Commission Model and WHO recommendation on the integration of PC implementation, two strategic approaches can be adopted by most countries. First is the long-term strategy of PC integration, which is referred to the Lancet Oncology Commission Model as the guidelines. Achieving this model requires time and resource investment, particularly in budget allocation (policy) and competencies (education). For example, Yamaguchi et al. stated that for obtaining certification for specialist PC, health professionals in the Asia-Pacific region need three (Australia, New Zealand, Malaysia, Singapore, and India) to four (Hong Kong) years (102). In addition, increasing specialization PC competencies are often too expensive for professionals living and working in LMICs (23). Moreover, the unstandardized palliative medicine education might contribute to variability in the content and quality of care delivered (103). While an intense collaboration between health and education sectors is needed to reform undergraduate and postgraduate curricula in palliative medicine, taking lectures/courses and conferences is suggested to gain more knowledge in PC.

The short-term strategy of PC integration (the WHO recommendation) can be implemented based on a country's existing resources (104). Characteristics of the health care system in most LMICs are commonly described as a lack of skilled health workers, lack of financial protection for the costs of health care, and health care service providers through primary health care (PHC) (105). PHC offers a cost-effective approach to achieving UHC; however, PHC in many LMICs is weak and often fails to provide comprehensive, patient-centered, integrated care (105). Despite its weaknesses, PHC's sufficient coverage area in the community is considered an essential advantage in the PC development process, especially for rural areas (106). As expanding infrastructure and provision following western countries' systems would be too expensive, too long to develop, and impractical for most LMICs, a PC community-based and/or palliative oncology-based approach is recommended (95).

The community-based PC meets LMICs' cultural aspects, e.g., strong familial bonds and social support. For a successful PC service implementation, it is important to understand the capacity and needs of the community to expand sustainable care. Home-based care is the best way of achieving good quality care and coverage in LMICs with strong family support but a poor health infrastructure (27). Similarly, our findings showed that home- and hospital-based PC was the common model reported in the systematic review among developing countries (73). Coverage is a key component in PC service delivery. PHC/community care is essential to provide PC service to the large majority in need who commonly live in a community or rural area where health care services are provided by generalists and not specialist practitioners (27). A Belgian qualitative study stated that PC does not necessarily equate to the need for specialist PC services but rather to the need for an approach embodying PC's principles, which regular care providers may provide with basic PC skills (19). Nevertheless, a review assessing PC in a rural areas of some HICs showed that community/home-based PC provided more access and services to those in need (106). The palliative oncology-based approach can also be a potential option, as the oncology unit is a common cancer service provider in most countries (73). However, studies suggested that hospital-based PC should focus more on outpatient, combine with home-visit, and link to community-based PC to be more efficient in PC service delivery (21, 87, 95). Regardless of community- or palliative oncology-based approach, a routine QOL assessment and a PC minimum essential package recommended by the WHO needs to be included (107), routine training on PC should be scheduled for community health workers, and empowering caregivers/communities (23, 27, 58). An Indonesian study pointed out that family caregivers can increase QOL of cancer patients in PC after receiving basic skill training that consists of educational packages on assisting a patient (58). Therefore, in countries with limited-resource settings in health care systems, the implementation of PC for all is feasible if the short- and long-term strategy is followed.

2.3. Strengths and limitations

This thesis has strength in terms of methodological aspects. The systematic review summarized potential factors influencing the QOL of advanced cancer patients in PC units in developing countries and followed the PRISMA statement's standard systematic review protocol. Also, the systematic review provided information on important variables that need to be included in the prospective cohort study. In the prospective cohort study, we used a standardized and validated QOL questionnaire of the EORTC Quality of Life Group to measure the outcome of interest in our study population that could prevent social desirability bias. In addition, all responses in the EORTC QLQ-C15-PAL were asked in the last seven days or one week before the assessment date which might hinder the recall bias.

Several limitations exist in this thesis. Despite a comprehensive predefined search strategy and multiple sources of suitable electronic databases in the systematic review, the search strategy was restricted to articles in English. Moreover, publication bias is possibly due to a tendency of studies with no association being commonly less published. Even though the prospective cohort study site is the national referral cancer hospital in Indonesia, only one group of patients was assessed in the cohort study. Therefore, the findings might not represent other cancer types and stages. Moreover, patients with a poor conditions in the prospective cohort study refused to participate, leading to under-representation of lower QOL scores. However, this study was proficient enough to describe QOL assessment within the population in this context.

2.4. Conclusions

The thesis showed that several socio-demographic characteristics (older patients > 65 years, married/ever married, and high educational level), cultural perspectives (used CAM and practiced spiritual/religious activities), and some QOL domains of the EORTC QLQ-C15-PAL (emotional functioning, fatigue, pain, insomnia, and appetite loss) influence the QOL of advanced cancer patients in PC. Therefore, specialists should focus on these specific QOL domains to increase patients' QOL in this health care facility. In addition, QOL assessment of advanced breast cancer patients in palliative oncology settings is necessary and feasible, despite the limited resource of health care services. Regardless of the models of PC integration (primary, secondary, or tertiary health care level), QOL should be routinely assessed in all level providers. Moreover, assessing QOL in PC is considered a patient-centered approach that is a key component in the concept of

UHC. The QOL assessment of advanced cancer patients in PC offers several advantages: contributing to the increase of health professionals' understanding of patients' symptoms burden or experiences and increasing the evidence-based research. Consequently, QOL assessment can be a medium for facilitating communication between patients and health care providers during consultations and as patient's preferences, expectations, and values in planning their cancer treatment. As strengthening PC implementation is most likely possible if the short- and long-term strategy of PC integration can be consistently implemented; therefore, PC for all as part of UHC can be achieved through a simple QOL assessment.

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4. Theses

1) Research on the quality of life of advanced cancer patients in palliative care settings in low- and middle-income countries, particularly in Indonesia, is considerably limited.
2) In developing countries, cancer patients in palliative care who were older (> 65 years), married or ever married, had high educational level, used complementary and alternative medicine, and practiced spiritual/religious activities were more likely to have a better quality of life and/or quality of life domains.
3) Cultural aspects are often a key factor influencing the quality of life of advanced cancer patients in palliative care in many countries where different ethnicities, religions, and cultural backgrounds exist.
4) Quality of life domains: physical scales (emotional functioning) and symptom scales (fatigue, pain, insomnia, and appetite loss) of the EORTC QLQ-C15-PAL were associated with quality of life score in patients with advanced breast cancer prior to their palliative oncology treatment.
5) Health care professionals need to focus on these specific domains of the EORTC QLQ-C15-PAL to improve quality of life.
6) A routine quality of life assessment can increase research interest, provide a patient-centered approach that leads to palliative care for all as part of Universal Health Coverage's concept, and facilitate palliative care integration into a country's health care system.

Publications

List of publications

1. Gayatri D, Efremov L, Kantelhardt EJ, Mikolajczyk R. Quality of life of cancer patients at palliative care units in developing countries: systematic review of the published literature. Qual Life Res. 2021;30:315–343.
2. Gayatri D, Efremov L, Mikolajczyk R, Kantelhardt EJ. Quality of life assessment and pain severity in breast cancer patients prior to palliative oncology treatment in Indonesia: a cross-sectional study. Patient Prefer Adherence. 2021;15:2017-2026.

Publication 1

The following article [Gayatri et al., Qual Life Res. 2021] has been published under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) that permits unrestricted use, distribution, and reproduction in any medium under specification of the authors (see the article) and the source (Qual Life Res, DOI: 10.1007/s11136-020-02633-z). The link back to the article on the publisher's website is https://link.springer.com/article/10.1007/s11136-020-02633-z. No changes were made.

Contribution as an author:

I have contributed to the conception and design of the work, formulation of the review questions, systematic review protocol development and registration, conducting the literature search in all electronic databases, selecting studies per protocol, appraising studies per protocol, extracting data, results analysis, interpretation of results, and writing the manuscript. In addition, I was responsible for the whole submission process until the manuscript was published.

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REVIEW

Quality of life of cancer patients at palliative care units in developing countries: systematic review of the published literature

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Abstract

Purpose This systematic review aims to summarize factors that influence the quality of life (QOL) of advanced cancer patients in palliative care (PC) in developing countries. Understanding this context in developing countries milieu is necessary; however, this outcome is rarely reported.

Methods Following the PRISMA guidelines, the electronic databases MEDLINE, Embase, CINAHL, and Web of Science were systematically searched using the search terms: QOL, cancer, PC, and names of all developing countries. Studies with less than ten subjects, qualitative or pilot studies, reviews, conference abstracts, and that reported validation of QOL questionnaires were excluded.

Results Fifty-five studies from 15 developing countries in the African ($n=5$), Latin America and the Caribbean ($n=10$), and Asian ($n=40$) region were included in the narrative synthesis. 65.4% were cross-sectional, 27.3% were cohort studies, 7.3% were RCTs or quasi-experimental studies. Around 30 QOL factors were studied with 20 different types of QOL instruments. Advanced cancer patients who were older, married/ever married, participated in additional care within PC, used complementary and alternative medicine (CAM), and practiced spirituality/religiosity showed higher QOL score. Low educational level and high depression were associated with a lower QOL.

Conclusion Various factors affect QOL among cancer patients in PC. Patients valued the use of CAMs; however, the quality and safety aspects should be properly addressed. Important factors that influenced the QOL score were social and spiritual support. While there is a general need to develop PC strategies further, recognizing patients' needs should be prioritized in national cancer programs.

Keywords Systematic review · Quality of life · Palliative care · Advanced cancer · Developing country

Introduction

Cancer remains a major public health problem in the world. In 2040, it is expected that 16.3 million people will live with cancer, most of them from low- and middle-income countries [1]. In these countries, the diagnosis for most cancers is frequently made at advanced stages when treatment options are limited or not accessible [2]. Cancer symptoms and treatment negatively affect patients' quality of life (QOL) because of physical discomfort, mental stress, and economic pressure [3–6]. Therefore, in 1990 the World Health Organization (WHO) introduced the palliative care (PC) initiative, which represents medical care focused on improving the QOL of patients with a severe illness by treating symptoms through an interdisciplinary approach [7, 8]. PC improves QOL through prevention and relief of suffering by assessment, early identification, and treatment of pain, helping

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with physical or psychosocial problems, and providing spiritual support [8]. Cancer patients often continue treatments that no longer provide benefit to their health status, instead of aligning treatment strategies to improve their QOL. An effective PC strategy can provide appropriate support and symptom control for cancer patients [9].

PC and its accessibility remain limited in developing countries and certain considerations, such as differences between the needs of specific countries, cultural differences, different healthcare capacity and organization have to be taken into account [2]. Better understanding of the factors that improve cancer patients' QOL in developing countries would be highly beneficial for initiating and/or strengthening PC implementation. However, most PC research originates from developed countries. Therefore, our systematic review aims to summarize evidence from the published literature on factors influencing cancer patients' QOL in PC settings in developing countries.

Methods

We followed a standard systematic review protocol, detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10] and registered our systematic review with PROSPERO (CRD42019142567).

Search strategy

We identified studies by searching MEDLINE, Embase, CINAHL, and Web of Science electronic databases. Search terms included 'quality of life', 'cancer', 'palliative care', and names of all developing countries. We followed the list of developing countries as published on the United Nations website (Online Resource 1) [11]. We used a broad search strategy to ensure a comprehensive review of the evidence and to capture all pertinent evidence. We supplemented our search strategy by manually reviewing references in the retrieved articles. We restricted our search to articles published in English between 1 January 1990 and 12 February 2019. The year 1990 was chosen, due to being the year of the WHO Palliative Care Initiative announcement [7].

Eligibility criteria and study selection

Two reviewers performed the selection of studies. Studies were considered for an initial review if they met the following inclusion criteria: adult patients (≥ 18 years) with advanced cancer stage, in PC Units (PCUs), in developing countries, and assessing QOL/QOL domains as the outcome of interest. The advanced cancer stage was defined accordingly to the American Joint Committee on Cancer staging criteria [12]. PC is defined by the WHO as medical or non-medical methods meant not to cure, but to offer a support system for patients to live their life as actively as possible until death; any form of treatment that concentrates on reducing a patients' symptoms or treatment-related side effects, improving QOL, and supporting patients and their families [13]. The primary outcomes were: (1) QOL score measured by QOL questionnaires [e.g. the European Organization of Research and Treatment for Cancer Quality of Life Questionnaire (EORTC QLQ), or the Functional Assessment of Cancer Therapy-General (FACT-G)]; (2) QOL domains e.g. functional scales (physical, role, emotional, cognitive, social functioning), symptoms scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties); or (3) symptoms/spirituality clusters, or specific symptoms (depression and anxiety).

The following exclusion criteria were used: studies with less than ten patients, qualitative or pilot studies, reviews, conference abstract, studies that included patients diagnosed with psychological disorders, and those that reported validation of QOL questionnaires. After removal of duplicates, titles and abstracts were screened by two authors independently (DG and LE), followed by assessment of the full text for selected studies to determine compliance with the inclusion criteria. Any disagreements were settled through discussion until a consensus was reached.

Data extraction and quality assessment

The two reviewers independently extracted data from each study (year of publication, region, country, study design, population demographics, study sample size, cancer type, PCUs, reported factors linked to QOL/QOL domains, score of QOL/QOL domains, reported outcome of interest, and study quality assessment), and entered it in a standardized data extraction matrix. Factors that were positively or negatively associated with QOL/QOL domains are presented in a narrative synthesis. Outcomes including QOL score, as measured by the global health status of the EORTC-QLQ, overall well-being subscales, or overall mean QOL of the FACT-G were extracted. Data on other QOL domains, and symptoms/spirituality clusters, or specific symptoms were extracted when available. We performed critical appraisal using the quality assessment scale for cross-sectional studies [14], the Newcastle–Ottawa Quality Assessment Scale for cohort studies [15], and the risk of bias assessment tool by the Cochrane collaboration for randomized control trials (RCTs) or quasi-experimental studies [16] as described in more detail in Online Resource 2.

Results

Study selection

The systematic search retrieved 1698 articles, after duplication removal 1439 articles (Fig. 1) were eligible for title and abstract screening using the predefined inclusion and exclusion criteria (Online Resource 1). We eliminated 1321 articles for not meeting the inclusion criteria. After screening the full text of 118 articles, 70 articles were excluded. Another seven articles were identified by searching reference lists of included articles. In total, 55 articles were included.

Study characteristics and quality assessment

The number of advanced cancer patients analyzed in the selected studies ranged from 16 [17] to 1245 [18]. The most common study design was cross-sectional (36 studies), followed by 15 cohort studies, 2 RCTs, and 2 quasi-experimental studies. These studies were from 15 developing

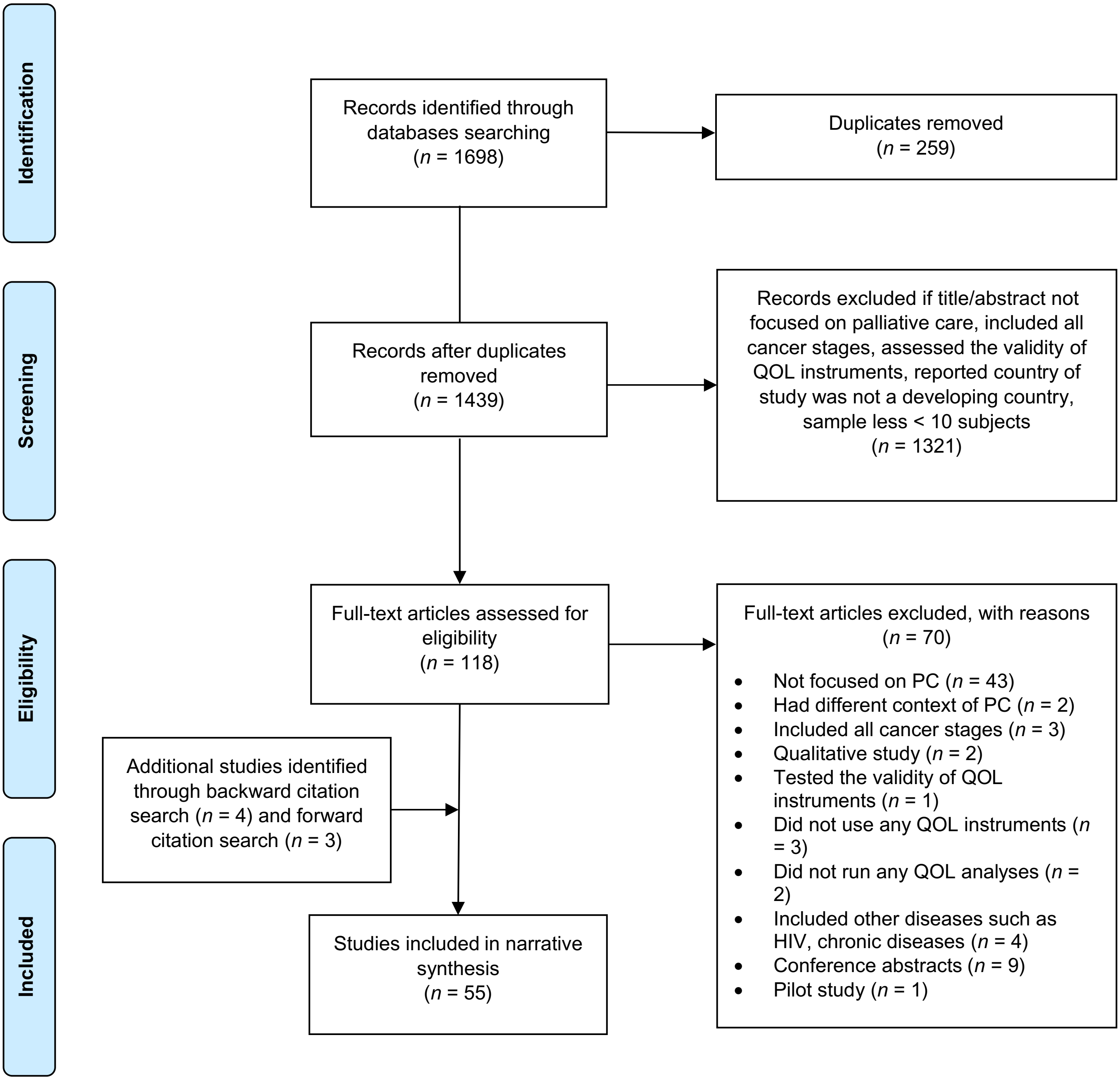


Fig. 1 PRISMA flow diagram of study collection. *Source* Moher et al. [10]

countries in the African region (Ethiopia, Kenya, and Malawi), Latin American and the Caribbean region (LAC) (Brazil), and Asian region (China, India, Indonesia, Jordan, Lebanon, Malaysia, Saudi Arabia, South Korea, Taiwan, Thailand, and Turkey). Geographically, most studies were from Asia ($n = 40$), followed by LAC ($n = 10$), and Africa ($n = 5$) (Table 1). Brazil, China, and India were countries with the highest number of studies (10, 9, and 9, respectively). While QOL research in developing countries were mostly conducted in hospital-based PC ($n = 50$), five studies did research on home-based PC (Online Resource 3). The results for cancer types and different QOL instruments are described in Online Resource 3. The quality assessment showed that from 36 cross-sectional studies, most studies ($n = 32$) had a low score (Table 1). Similarly, 2 of 4 RCTs and quasi-experimental studies had a low score. Only 5 of 15 cohort studies had a high score, as described in Online Resource 4.

Factors associated with QOL in PCUs

Around 30 factors were reported in the 55 included studies (Table 2). These studies showed that factors assessed and linked to QOL/QOL domains in developing countries varied across the African, LAC, and Asian region (Tables 3, 4).

Sociodemographic factors

The patients age ranged from 18 [19] to 94 years [20]. Studies from Africa [19] and Asia [18, 20–24] showed that older patients (> 65 years) had better QOL/QOL domains (psychological, existential, and support) compared to other age groups, which was related to positive coping mechanisms and social support from family and friends [20–22]. The reported gender proportions varied among the studies. While six studies showed that the proportion of male patients was higher than of female patients [9, 20, 22, 25–27], two studies demonstrated the opposite [23, 24]. Six Asian studies [9, 20, 23–26] reported that female cancer patients had better QOL/QOL domains (constipation or dyspnea in symptom function, physical functioning, sexual functioning, support, or spirituality clusters) than male patients, while one study in India [27] and one in South Korea [22] found the opposite results. Gielen et al. stated that in Indian tradition, women acted as the central providers of care in the families [27]. Having a life-threatening illness often results in the loss of the care role in the family, and contributes to a more distressing situation for Indian women [27]. In contrast, Taiwanese culture considered men as breadwinners and decision-makers in the family [25]. Therefore, family members often try to prolong a male patient's life by sending them to the hospital for additional treatments, despite their terminal condition. Female cancer patients in Taiwan tended to receive PC at home and experienced a better QOL compared to male cancer patients [25]. Personality differences between male and female cancer patients were considered a key factor for the observed discrepancy [24]. Women were more expressive in their needs, more willing to seek and receive help from others compared to men. Consequently, they often received more support, which contributed to a better QOL [24].

Our review indicated that sociodemographic factors e.g. marital status (married/ever been married), number of children (> 4 children) [26], education (high level) [19, 26, 27], occupation (formal employment) [19], and income (high) [19] were linked to better scores in QOL/QOL domains. Evidence showed that patients who lived with family/spouse/children/parents were more likely to have better QOL/low score of depression and anxiety compared to those who lived alone [20, 22, 28]. Patients, who lived with a spouse, often received psychological and financial supports during their illness, which positively influenced their QOL [20, 22]. Moreover, patients with unsupported family members had a high score on anxiety and depression and subsequently poor QOL [28]. Only one study that assessed the association between the number of children and QOL reported that patients having > 4 children tended to have better QOL [26]. Children were considered as one of the key caregivers in developing countries' culture, since taking care of sick parents is seen as a responsibility and not a burden [26]. A low proportion of cancer patients had a high level of education (range from 10 to 15.7%) [19, 27]. Low educational level was associated with decreased disease awareness, late screening, and late-stage diagnosis which leads to poor prognosis and low score of QOL [19]. Moreover, Gielen et al. reported that less-educated cancer patients often had low socioeconomic status (SES) in society [27]. As a consequence, they were more likely to have limited understanding of their disease, to show symptoms of depression, and have poor QOL [27]. Better education of patients is often linked to better job opportunities. For example, 17% of cancer patients who had formal employment tended to have higher social, psychological, spiritual, and QOL scores compared to those who were farmers and casual worker [19]. While formal employment was associated with adequate social support based on high-income earnings, low income was linked to poverty, low SES, and limited access to health care [19].

Important factors in clinical setting

Patients who underwent medical treatment e.g. chemotherapy cycles [17], palliative radiotherapy [29–31], and symptoms management therapy particularly for pain and fatigue [8, 18, 22, 24, 32–40], had positive association between these factors and QOL/QOL domains. For example, an Indian cohort study reported that short-course palliative radiotherapy schedule for inoperable head and neck

Table 1 Characteristics of included studies

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Africa ($n = 5$)										
Bates et al., 2015 [78]	Malawi	Cross-sectional	N/A	72	Mean (min–max) 49.5 (20–80)	F: 72 (100%)	Cervical cancer 72 (100%)	Hospital-based	(cancer-related) Symptoms	Low
Kamau et al., 2007 [79]	Kenya	Cross-sectional	EORTC-QLQ-C30	152	20–29 = 7 (4.6%); 30–39 = 18 (11.8%); 40–49 = 45 (29.6%); 50–59 = 47 (30.9%); 60–69 = 26 (17.1%), ≥ 70 = 9 (5.9%)	F: 152 (100%)	Cervical cancer 152 (100%)	Hospital-based	Global health status	Low
Lakew et al., 2015 [54]	Ethiopia	Cross-sectional	Custom instrument	403	Mean (SD) 45.8 (11.3); < 35 = 41 (10.7%), ≥ 35 = 343 (89.3%)	N/A	All cancer types	Hospital-based	Physical well-being, social/family well-being	Low
Ogoncho et al., 2016 [55]	Kenya	Cross-sectional	MVQOLI	108	Mean (SD) 49.1 (4.1); min–max 18–71	F: 108 (100%)	Gynecological cancer: cervical 60 (56%), ovarian 26 (24%), endometrial 21 (19%)	Hospital-based	Overall QOL	Low
Ogoncho et al., 2015 [19]	Kenya	Cross-sectional	MVQOLI	108	Mean (min–max) 48 (18–72); 18–24 = 9 (8%); 35–55 = 39 (36%); 45–54 = 19 (18%); 55–64 = 22 (20%); > 65 = 19 (18%)	F: 108 (100%)	Gynecological cancer: cervical 60 (56%); ovarian 26 (24%); endometrial 21 (19%)	Hospital-based	Total QOL	Low
Latin America and the Caribbean ($n = 10$)										
Alfano et al., 2014 [41]	Brazil	Cross-sectional	EORTC QLQ-C30; EORTC QLQ-BR23	126	Mean (SD) 51.4 (10.9)	F: 126 (100%)	Breast cancer 126 (100%)	Hospital-based	Global health status	Moderate
Avelino et al., 2015 [17]	Brazil	Cohort	EORTC QLQ C-30; QLQ-LC13	16	Median 63.7; < 65 = 6 (37.5%); ≥ 65 = 10 (62.5%)	F: 7 (43.8%); M: 9 (56.3%)	Non-small cell lung carcinoma 10 (62.5%)	Hospital-based	Global health status	Moderate
Camargos et al., 2015 [45]	Brazil	Cross-sectional	WHOQOL-Bref	525	< 30 = 13 (2.5%); 30–60 = 294 (56%); > 60 = 218 (41.5%)	F: 243 (46.3%); M: 282 (53.7%)	All cancer types 525 (100%)	Hospital-based	Overall QOL	Moderate

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Carmo et al., 2017 [53]	Brazil	Intervention	EORTC QLQ-C15-PAL	63	Mean 52.9	F: 41 (65.1%); M: 22 (34.9%)	Breast cancer 18 (28.6%); cervix 9 (14.3%); colon and rectum 7 (11.1%); lung 7 (11.1%)	Hospital-based	Global health status	High
Mendes et al., 2014 [35]	Brazil	Cross-sectional	WHOQOL-BREF	56	Median (min–max) 65.5 (28–92)	F: 31 (55.4%); M: 25 (44.6%)	Gastrointestinal tract 20 (30.7%), respiratory tract 8 (14.3%), genitourinary tract 8 (14.3%), head and neck 6 (10.7%)	Hospital-based	QOL domains: physical, psychological, social relationships, environment	Low
Mendez et al., 2017 [36]	Brazil	Cohort	EORTC QLQ-C30, EORTC QLQ-BM22	35	Mean (min–max) 56 (22–80)	F: 23 (66%); M: 12 (34%)	Breast cancer 11 (31.4%), prostate 6 (17.1%)	Hospital-based	Global health status	Moderate
Paiva et al., 2012 [8]	Brazil	Cohort	ESAS	232	Median (min–max) 59 (18–88); mean (SD) 58.9 (12.8)	F: 112 (48%); M: 120 (52%)	Gastrointestinal 56 (24%); breast 41 (17%)	Hospital-based	Total symptom distress score (TSDS); symptoms score	High
Rigoni et al., 2016 [80]	Brazil	Cross-sectional	EORTC QLQ-C30; Coop/Wonca questionnaire	30	Mean 56.6	F: 2 (6.7%); M: 28 (93.3%)	Oropharynx 11 (36.7%); larynx 10 (33.3%)	Hospital-based	Global health status	Moderate
Rugno et al., 2014 [56]	Brazil	Cohort	EORTC QLQ-C30	87	Median (min–max) 56 (24–83); < 45 = 21 (24.1%); 45–65 = 50 (57.5%); > 65 = 16 (18.4%)	F: 87 (100%)	Breast 50 (50.7%); cervix 19 (21.8%); ovarian 14 (16.0%)	Hospital-based	Global health status	High

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Rafael da Silva Ribeiro et al., 2015 [38]	Brazil	Cross-sectional	EORTC QLQ-C30	63	Median (min–max) 62 (33–84) patients in hospital-based PC vs 70 (49–90) in home-based PC	F: 38 (60.3%); M: 25 (39.7%)	Breast cancer 10 (15.9%), uterine cervix 6 (9.5%)	Hospital-based	Global health status	Low
Asia (n = 40)										
Das et al., 2013 [29]	India	Cohort	FACT H and N	33	Mean (min–max) 57.8 (34–75)	F: 4 (12%); M: 29 (88%)	Head and neck cancer: oral cavity 11.9 (36%); hypopharynx and laryny 11.2 (34%)	Hospital-based	Physical, social, emotional, functional well-being	Moderate
Gandhi et al., 2014 [32]	India	Cross-sectional	EORTC QLQ-C15-PAL	100	Median (min–max) 55 (22–80)	F: 17 (17%); M: 83 (83%)	Head and neck cancer: oropharynx 46%; oral cavity except tongue 19%	Hospital-based	Global health status	Low
Ghoshal et al., 2016 [33]	India	Cohort	EORTC QLQ-C15-PAL	500	Median (SD) 52 (13.1); < 20 = 3 (0.6%); 21–40 = 101 (20.2%); 41–60 = 272 (54.4%); 61–80 = 118 (23.6%); > 80 = 6 (1.2%)	F: 204 (50.8%); M: 258 (51.6%)	Head and neck 116 (23.2%); gastro intestinal 106 (21.2%); gastro urinary 87 (17.4%)	Hospital-based	Global health status	High
Gielen et al., 2017 [27]	India	Cross-sectional	Hindi 36 spirituality items (custom made)	300	Mean (SD) 47.5 (12.4)	F: 148 (49.3%); M: 152 (50.7%)	Breast cancer 45 (15%), lung 26 (8.7%), gallbladder 15 (5%), rectum 13 (4.3%)	Hospital-based	Spiritual distress clusters	Low

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Kandasamy et al., 2011 [47]	India	Cross-sectional	FACT-G, and FACT-pal	50	Mean (SD) 49.7 (10.2); min–max 17–64	F: 28 (56%); M: 22 (44%)	Oropharyngeal cancer 11 (22%), gynecological (cervix, endometrium, ovary) 11 (22%)	Hospital-based	QOL; subscales: physical well-being, social/family well-being, emotional well-being, functional well-being	Moderate
Mehta et al., 2008 [30]	India	Cohort	EORTC QLQ-C30	62	Mean (min–max) 62 (30–70)	F: 30 (48.4%); M: 32 (51.6%)	Carcinoma esophagus 62 (100%)	Hospital-based	Global health status	High
Prasad et al., 2015 [31]	India	Cohort	EORTC QLQ-C30	33	Median (min–max) 60 (35–78)	F: 12 (36.4%); M: 21 (63.6%)	Esophageal 33 (100%)	Hospital-based	Global health status	Moderate
Nayak et al., 2019 [37]	India	Cross-sectional	the QOL questionnaire version II (cancer institute quality of life questionnaire version II for cancer patients in India)	768	51–60 = 232 (30.2%); other age groups N/A	N/A	Head and neck cancer 308 (40.1%); breast/cervix/gastrointestinal tract/lung/colorectal were not reported in detailed	Hospital-based	General well-being score	Low
Palat et al., 2018 [81]	India	Cross-sectional	(unvalidated) POS, and HADS	76	Mean (SD) PC 48.6 (12.1) without contact to PC group vs 49.9 (16.2) with contact to PC group	F: 38 (50%); M: 38 (50%) both groups	Gastrointestinal 11 (14.4%); cervix 11 (14.4%); head and neck 10 (13.2%); lung 9 (13.2%)	Hospital-based	Pain intensity	Low
Aboshaiqah et al., 2016 [3]	Saudi Arabia	Cross-sectional	EORTC QLQ-C15-PAL	130	Mean (SD) 46.7 (16.5); min–max 17–86	F: 103 (79.2%); M: 27 (20.8%)	Breast cancer 69 (53.1%); colorectal 19 (14.6%); lung 15 (11.5%)	Hospital-based	Global health status	Moderate

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Abu-Saad Huijer et al., 2012 [82]	Lebanon	Cross-sectional	EORTC QLQ-C30	200	Mean (SD) 54 (13.6); min–max 19–86; 13–34 = 17 (8.5%); 35–54 = 87 (43.5%); ≥ 55 = 96 (48%)	F: 126 (63%); M: 74 (37%)	Breast cancer 89 (44.5%); gastrointestinal system 36 (18%); blood 20 (10%)	Hospital-based	Symptoms prevalance	Low
Al-Zahrani et al., 2014 [83]	Saudi Arabia	Cross-sectional	AQSA	124	Mean (min–max) 56 (20–92)	F: 51 (41%); M: 73 (59%)	Breast cancer 34 (27.4%); head and neck 19 (15.3%); genitourinary 16 (12.9%)	Hospital-based	Pain score	Low
Bulbul et al., 2017 [18]	Turkey	Cross-sectional	ESAS	1245	Mean (SD) 61.8 (9.4)	F: 141 (11.3%); M: 1,104 (88.7%)	Lung cancer 1,245 (100%)	Hospital-based	Well-being	Moderate
Shamieh et al., 2017 [57]	Jordan	Cohort	ESAS	298	Mean (SD) 52.7(13.7)	F: 86 (47%); M: 96 (52%)	Breast cancer 40 (22%); lung 37 (20%); gastro-intestinal 31 (17%)	Hospital-based	Symptoms	Moderate
Aamir et al., 2012 [28]	Malaysia	Cross-sectional	EORTC-QLQ-C30 and HADS	288	Mean (SD) 54 (15.7); min–max 20–85	F: 111 (38.5%); M: 177 (61.4%)	All cancer types	Hospital-based	Global health status	Low
Chaiviboontham, 2015 [42]	Thailand	Cross-sectional	SWBS	240	Mean (min–max) 56.1 (19–86)	F: 122 (50.8%); M: 118 (49.2%)	Gastrointestinal, breast, hepatobiliary, lung (no number reported)	Hospital-based	QOL	Moderate
Chan et al., 2012 [21]	China	Cross-sectional	MQOL-HK, HADS	53	Mean (SD) 62.11 (15.5); min–max 35–92	F: 53 (100%)	Gynecological cancer: ovary 29 (54.7%); cervix 13 (24.4%)	Hospital-based	Mean total QOL	Low
Chang et al., 2009 [25]	Taiwan	Cohort	SF-36	180	Mean (SD) 67.3 (13.1)	F: 57 (32%); M: 123 (68%)	Lung 39 (22%); colorectal 29 (16%); gastric 21 (12%)	Hospital-based	Survival time (as QOL proxy)	Moderate

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Chui et al., 2009 [20]	China	Cross-sectional	MQOL	300	Mean (min–max) 67.5 (21–94)	F: 136 (45.3%); M: 163 (54.3%)	Lung, gastrointestinal are the most common out of 9 primary site of cancer (no number reported)	Hospital-based	Total QOL, QOL single item	Moderate
Cui et al., 2014 [26]	China	Cross-sectional	MQOL	531	18–44 = 48 (9%); 45–59 = 145 (27.3%); 60–74 = 164 (30.9%), > 75 = 174 (32.8%)	F: 234 (44.1%); M: 297 (55.9%)	All cancer types	Hospital-based	QOL	Moderate
Deng et al., 2015 [52]	China	Cohort	MQOL	630	Median (min–max) 62 (20–78)	F: 282 (44.8%); M: 348 (55.2%)	Lung 203 (32.2%); liver 67 (10.6%); gastric 52 (8.3%)	Hospital-based	Overall QOL	High
Ezat et al., 2014 [84]	Malaysia	Cross-sectional	SF-36 QOL	120	Mean (min–max) 57 (22–83)	F: 63 (52.5%); M: 57 (47.5%)	Lung 40 (33.4%); breast cancer 24 (20%); colon 19 (15.8%)	Hospital-based	QOL	Low
Fan et al., 2011 [48]	China	Cross-sectional	EORTC QLQ-C30	173	Mean (SD) 61.13 (12); min–max 19–86	F: 79 (45.7%); M: 94 (54.3%)	Lung 71 (41.0%); gastrointestinal 24 (13.9%); liver pancreas 24 (13.9%)	Home-based	Global health status	Moderate
Kim, 2014 [22]	South Korea	Cross-sectional	MQOL (the McMaster Quality of Life	52	Mean 49.2	F: 13 (25.5%); M: 38 (74.5%)	Lung 15 (28.9%), stomach, liver, gall bladder and leukemia each 5 (9.6%)	Hospital-based	Overall QOL	Moderate

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Kim et al., 2013 [49]	South Korea	Cohort	EQ-VAS	262	Median (min–max) 60 (22–91)	F: 104 (39.7%); M: 158 (60.3%)	Colorectal 56 (21.4%); gastric 50 (19.1%); hepatobiliary 48 (18.3%)	Hospital-based	QOL	Moderate
Kristanti et al., 2017 [23]	Indonesia	Cohort	EORTC QLQ-C30	30	18–44 = 9 (30%); 45–54 = 10 (33%), > 55 = 11 (37%)	F: 22 (73%); M: 8 (27%)	Breast cancer 9 (30%); digestive (colon, recti, sigmoid) 5 (17%); gynecology (vulva, ovarian, cervical) 5 (17%)	Hospital-based	Global health status	High
Lau et al., 2013 [9]	China	Cross-sectional	QOLC-E	90	Mean (min–max) 64 (38–87)	F: 45 (50%); M: 45 (50%)	Respiratory 33 (36.7%); digestive-gastrointestinal 26 (28.9%); head and neck 10 (11.1%)	Hospital-based	Overall QOL; global QOL by single-item scale	Low
Lee et al., 2015 [34]	South Korea	Cohort	EORTC QLQ-C30	463	Mean (min–max) 57.3 (20–87)	F: 196 (42.3%); M: 267 (57.7%)	Stomach 83 (18%); colon 73 (15.8%); lung 67 (14.5%)	Hospital-based	Global health status	High
Lee et al., 2014 [85]	South Korea	Cohort	EORTC QLQ-C15-PAL	162	≥ 65 = 82 (50.6%); 40–65 = 75 (46.3%) < 40 5(3.1%)	F: 86 (53.1%); M: 76 (46.9%)	Lung 40 (24.7%); hepatobiliary 34 (21%); ovary/cervix of uterus 31 (19.1%)	Hospital-based	Physical functioning	Moderate
Lee et al., 2013 [50]	South Korea	Cohort	EORTC-QLQ-C30 and HADS	98	Mean (SD) 57.3 (10.9); 24–40 = 4 (4.1%); 41–60 = 50 (51.0%); 61–78 = 44 (44.9%)	F: 31 (31.6%); M: 67 (68.4%)	Stomach 44 (44.9%); lung 32 (32.6%)	Hospital-based	Overall QOL	Moderate

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Li et al., 2014 [86]	China	Cross-sectional	EORTC QLQ-C30	109	Mean (SD) 69 (7)	F: 43 (39.4%); M: 66 (60.6%)	Esophageal and gastric 44 (40.3%); lung 19 (17.4%); liver 11 (10.1%)	Hospital-based	Role functioning	Moderate
Lua et al., 2011 [43]	Malaysia	Cross-sectional	MQOL	39	Mean (min–max) 55.9 (27–82)	F: 22 (56.4%); M: 17 (43.6%)	All cancer types	Hospital-based	Global health status	Low
Pokpalagon et al., 2012 [44]	Thailand	Cross-sectional	MVQOLI	180	Mean (min–max) 55.2 (20–84)	F: 109 (60.6%); M: 71 (39.4%)	Breast 51 (28.3%); hepatobiliary 32 (17.8%); lung 26 (14.4%); colorectal 19 (10.6%)	Hospital-based and home-based	Overall QOL	Moderate
Shahmoradi et al., 2012 [87]	Malaysia	Cross-sectional	HQLI	61	Mean (SD) 59.2 (12.5) min–max 18–74	F: 33 (54%); M: 28 (46%)	Breast 11 (18%); colon 8 (13.1%); rectum 8 (13.1%)	Home-based	Mean total score	Low
Tang et al., 2016 [51]	Taiwan	Cohort	MQOL	325	<66 = 225 (69.2%); 66+ = 100 (30.8%)	F: 138 (42.5%); M: 187 (57.5%)	Stomach 61 (18.8%); liver 54 (16.6%); pancreas 49 (15.1%)	Hospital-based	QOL	High
Tsai et al., 2012 Taiwan [39]	Taiwan	Cohort	Custom made "symptom reporting form"	426	Median (min–max) 67 (27–93)	F: 212 (48.2%); M: 228 (51.8%)	Lung 89 (20.2%); liver 79 (18%); colon-rectum 47 (10.7%)	Hospital-based	Fatigue	Moderate
Wang et al., 2016 Taiwan [58]	Taiwan	Cross-sectional	FACT-G	85	Mean (SD) 59.5 (12.4)	F: 45 (52.9%); M: 40 (47.1%)	Gastrointestinal 24 (28.2%); head and neck, breast, and liver each 12 (14.1%)	Hospital-based	Total FACT-G score	Moderate

Table 1 (continued)

Author, year of publication	Country	Study design	Type of QOL questionnaire	Study sample size	Age	Sex	Type of cancer	PCUs	Reported outcome	Quality assessments
Wang et al., 2011 [40]	China	Cross-sectional	FACT-G	201	Mean (SD) 65.5 (12.8); min–max 30–89	F: 84 (41.8%); M: 117 (58.2%)	Colorectal 47 (23.4%); lung 40 (19.9%); esophageal and gastric 28 (13.9%)	Hospital-based	Total FACT-G score	Moderate
Yan, 2006 [24]	China	Cross-sectional	MQOL-HK	85	Mean (SD) 63.39 (13.2); min–max 39–93	F: 48 (56.5%); M: 37 (43.5%)	Lung 28 (32.9%); cervix/uterine/ovary 10 (11.7%)	Home-based	Total QOL score	Moderate
Yoon et al., 2018 [46]	South Korea	Cross-sectional	EORTC QLQ-C15-PAL	202	Mean 64.9	F: 99 (49.1%); M: 103 (50.9)	Lung 45 (22.3%); colon/rectal 41 (20.3%); liver/biliary tract 29 (14.4%)	Hospital-based	Overall QOL	Low

QOL quality of life, *PCUs* palliative care units, *N/A* not available, *F* female, *M* male, *SD* standard deviation, *EORTC-QLQ-C30* the European Organization for Research and Treatment of Cancer quality of life questionnaire of cancer patients, *EORTC QLQ-BR23* the European Organization for Research and Treatment of Cancer quality of life questionnaire of women with breast cancer, *EORTC QLQ-BM22* the European Organization for Research and Treatment of Cancer quality of life questionnaire of bone metastases, *EORTC QLQ-C15-PAL* the European Organization for Research and Treatment of Cancer quality of life questionnaire of palliative care, *MVQOLI* the Missoula Vitas Quality of Life Index, *WHOQOL-BREF* the World Health Organization quality of life instruments, *ESAS* the Edmonton Symptom Assessment, *FACT H and N* Functional Assessment of Cancer Therapy Head and Neck, *FACT-G* the functional assessment of cancer therapy-general, *FACT-pal* the functional assessment of cancer therapy-palliative care, *POS* the palliative care outcome scale, *HADS* the Hospital Anxiety and Depression Scale, *AQSA* the Arabic Questionnaire for Symptom Assessment, *SWBS* the spiritual well-being scale, *MQOL-HK* Mc Gill quality of life questionnaire Hong Kong Chinese version, *MQOL* the McMaster Quality of Life, *SF-36* Study Short-Form-36, *EQ-VAS* the EuroQoL-5 dimensions-visual analog scale, *QOLC-E* the quality of life concerns in the end of life questionnaire, *HQLI* the hospice quality of life index

Table 2 Factors associated with quality of life in included studies

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Africa ($n=5$)				
Bates et al., 2015 [78]	Palliative care interventions (pain medication)	Pain	N/A	N/A
Kamau et al., 2007 [79]	Patients' perception of diagnosis and treatment on palliative radiotherapy	N/A	Overall QOL; overall physical health	N/A
Lakew et al., 2015 [54]	Use of PC services (counseling services, service brochure and benefit, books and videos library, relaxation class, drop counseling and support service, 24 h telephone support and cancer advisory, home nursing service, perform home activities, monitory allowances)	Physical well-being; social/family well-being	N/A	N/A
Ogoncho et al., 2016 [55]	Specific additional care within PCUs (pain relief service, management of other symptoms, psychological counseling, spiritual care)	Total QOL; interpersonal subscale	N/A	Mean (SD) total QOL = 17.2 (0.4); interpersonal subscale 5.3 (1.1)
Ogoncho et al., 2015 [19]	Age (> 65), occupational (formal employment status), monthly income (> 10,000 Kenyan shillings or equal to 99 US$), level of education (high), type of gynecological cancer, type of historic received cancer treatment	Total QOL	N/A	Positive improvement in mean (SD): age group 18–24 = 17 (1.2); 35–44 = 16 (3.3); 45–54 = 16 (4.1); 55–64 = 7 (4.7); > 65 = 21 (3.3); occupation: housewife = 6 (4.5); peasant farmer = 16 (4.7); casual worker = 16 (1.6); self-employed = 18 (3.6); formal employment = 20 (3.2)
Latin America and the Caribbean ($n=10$)				
Alfano et al., 2014 [41]	Body-mind interventions (meditation, yoga, acupuncture, relaxation, prayer, hypnotherapy, psychotherapy, and art therapy) as one of complementary and alternative medicine (CAM)'s modalities	Sexual enjoyment; perspective for the future	Cognitive function	Median (P25-P75) sexual enjoyment = 66.7 (33.3–100); future perspective = 0.0 (0.0–66.7); cognitive function $n=66.7$ (50.0–100)
	Biologically based practices (medicinal herbs, vitamins, minerals, food supplements, and probiotics) as one of CAM's modalities	N/A	More frequent constipation	Median (P25-P75) constipation $n=0.0$ (0.0–33.3)

Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Avelino et al., 2015 [17]	Chemotherapy cycles	Physical function; congnitive function; cancer-related symptoms e.g. pain, and appetite loss	N/A	Mean ± SD, median physical function $n = 59.8 \pm 27.7$, 60.0 to 81.5 ± 20.9, 93.3; cognitive function $n = 79.0 \pm 35.9$, 100.0 to 73.1 ± 30.1, 83.3; pai $n = 60.4 \pm 35.4$, 58.4 to 78.2 ± 23.9, 83.3; appetite loss $= 41.7 \pm 46.4$, 16.5 to 79.5 ± 39.8, 100.0
Camargos et al., 2015 [45]	Spirituality/religiosity (connection, meaning in life, admiration, wholeness and integration, spiritual strength, inner peace, hope and optimism, faith)	Global QOL; social domain; environmental domain	N/A	Mean (SD) global QOL = 78.0 (16.8); social domain $n = 77.6$ (17.2); environmental domain $n = 75.8$ (15.6)
Carmo et al., 2017 [53]	Psychosocial intervention based on the cognitive-behavioral therapy (CBT) techniques (psychoeducation on patient's current clinical condition and the purpose of palliative care, the functioning of anxiety, technique to manage symptoms, and techniques for the detection and questioning of automatic thoughts as well as their influence and essential role in the triggering of emotions and behaviors)	Global health status	N/A	Mean (SD) global health status Arm A (received psychological intervention, received early PC intervention) = 76.3 (17.0); Arm B (received early PC intervention) = 72.7 (25.5); Arm C (standard cancer treatment) = 66.7 (29.5)
Mendes et al., 2014 [35]	Pain intensity	Environment domain	Physical domain	Scale value range from 0–100 environmental domain $n = 70.7$; physical domain $n = 51.3$
Mendez et al., 2017 [36]	Pain changes	Global health status	N/A	Median (IQR) global health status = 66 (50–100) to 33 (16–66)
Paiva et al., 2012 [8]	Anorexia, fatigue, nausea, pain, depression and anxiety, drowsiness, well-being, dyspnea	N/A	Total symptom distress score (TSDA)	Positive improvements in patients: anorexia = 90; fatigue = 112; nausea = 57; pai $n = 133$: positively improved from baseline and follow-up; depression $n = 102$; anxiety = 121; drowsiness = 98; well-being = 128; dyspnea = 56; TSDA = 232

Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Rigoni et al., 2016 [80]	Patients' perception of pain, difficulty to detect problems, problem with social contact, use of analgesics, weight loss	N/A	Global health status	Mean ± SD, median global health status = 54.17 ± 24.93, 58.33
Rugno et al., 2014 [56]	Integrated care model (ICM)	Global health status; emotional functioning; social functioining; insomnia	N/A	Median score for global health status = 66.6; emotional functioning = 66.6; social functioning = 83.3; insomnia = 33.3
Rafael da Silva Ribeiro et al., 2015 [38]	Home-based palliative care	Global health status; functional scale; most of symptoms (except insomnia and diarrhea)	N/A	Global health status score (range from 0–100) = 57.1
Asia (n = 40)				
Das et al., 2013 [29]	Hypofractionated palliative radiotherapy (short duration)	Social well-being	N/A	Positive improvement: social well-being = 17.4 to 20.0
Gandhi et al., 2014 [32]	Symptoms, emotional functioning, physical functioning	Global health status	N/A	Mean global health status = 50.84
Ghoshal et al., 2016 [33]	Fatigue changes	Overall QOL; physical functioning; insomnia	N/A	Median (SD) Overall QOL = 50.0 (21.15) to 66.7 (26.58); physical function = 46.7 (24.08) to 60.0 (26.51); insomnia = 33.33 (30.98) to 0 (22.79)
Gielen et al., 2017 [27]	Sex (male), educational level (high), pain score (low)	(patients) Spirituality distress clusters	N/A	N/A
Kandasamy et al., 2011 [47]	Spiritual well-being	QOL; physical well-being; social family well-being; emotional well-being; family well-being; palliative well-being	N/A	N/A
Mehta et al., 2008 [30]	Combined palliative radiotherapy (intraluminal brachytherapy and external radiation)	Global health status	N/A	Mean QOL score Arm A (30 Gy/10 fractions/2 weeks XRT + 12 Gy ILBT (600 cGy per session × 2)) = 38 to 56; Arm B (30 Gy/10 fractions/2 weeks XRT) = 30 to 55; Arm C (20 Gy/5 fractions/1 week XRT) = 24 to 37
Prasad et al., 2015 [31]	Palliative radiotherapy	Global health status; dysphagia	N/A	Mean (SD), median global health status = 107.5 (10.1), 106 to 114.1 (7.5), 116; dysphagia = 4.1 (1.2), 4 to 2.4 (1.1), 3
Nayak et al., 2019 [37]	Symptoms, cognitive well-being (good), economic status (high)	Body image	QOL; physical and psychological domains	general well-being total score (mean ± SD) 32 (10.65 ± 3.23)
Palat et al., 2018 [81]	Contact with PC units	N/A	Pain	N/A

Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Aboshaiqah et al., 2016 [3]	Satisfaction care	Emotional function	N/A	N/A
Abu-Saad Huijer et al., 2012 [82]	Cognitive functioning	Global health status	N/A	Mean (SD) global health status = 58.46 (23.86)
Al-Zahrani et al., 2014 [83]	Age, sex, type of cancer, performance status, type of encounter in PC	Pain intensity	N/A	N/A
Bulbul et al., 2017 [18]	Age, body weight, weight loss, metastasis, symptom distress (pain, tiredness, drowsiness, lack of appetite, shortness of breath, depression, anxiety)	N/A	Well-being	N/A
Shamieh et al., 2017 [57]	Initial consultation provided by PC team	Symptoms: pain; fatigue; nausea; depression; anxiety; drowsiness; appetite; well-being; dyspnea; and sleep	N/A	Mean (SD) pain = 7 (1.8) to 6 (2.8); fatigue = 7 (1.8) to 6 (2.5); nausea = 7 (2.0) to 4 (3.7); depression = 7 (1.9) to 5 (3.2); anxiety = 7 (2.0) to 5 (3.0); drowsiness = 6 (1.7) to 5 (2.7); appetite = 7 (1.9) to 6 (3.0); well-being = 7 (1.8) to 6 (2.6); dyspnea = 6 (1.8) to 5 (3.2); sleep = 7 (1.8) to 5 (2.7)
Aamir et al., 2012 [28]	Depression, anxiety	N/A	Global health status	Mean ± SD global health status = 35.5 ± 10.9 (for depression); global health status = 34.3 ± 12.2 (for anxiety)
	Family function	N/A	Global health status	Mean ± SD global health status = 80.5 ± 14.7
Chaiviboontham, 2015 [42]	Spiritual well-being, a combination of PC strategy (pharmacological and psychosocial care, mind–body intervention, and spiritual care; physical management; and traditional medicine, herbs, and diet management)	QOL	N/A	N/A
Chan et al., 2012 [21]	Age (older)	QOL	N/A	Mean total score QOL = 0.683
	Depression, and anxiety	N/A	QOL	Mean total score QOL = -0.518 (for depression); Mean total score QOL = -0.278 (for anxiety)
Chang et al., 2009 [25]	Sex (female), KPS (high), overall symptoms severity (low)	N/A	Survival time (as a proxy of QOL)	N/A

Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Chui et al., 2009 [20]	Age (older), sex (female), marital status (had ever been married), physical functioning (higher)	QOL score	N/A	Mean total score QOL = 6.2 (range 0–10)
Cui et al., 2014 [26]	Sex (female), educational level (university +), number of children > 3), awareness of the disease (not aware at all), hospital size (tertiary)	MQOL total score	N/A	Mean ± SD QOL = 5.09 ± 0.90
Deng et al., 2015 [52]	Specific additional care within PCUs	QOL domains (physical, psychological, physical well-being, depressed, anxious, sad, fear of future, seeing life as a burden, existential well-being, personal existence, achieving life goals, life is worthwhile, self-content, closeness to people, world is caring, dignity, support, eating, sex); overall QOL	N/A	Mean (SD) physical = 6.21 (1.51) to 4.16 (2.06); psychological = 5.99 (2.05) to 4.89 (2.17); physical well-being = 7.03 (1.96) to 5.90 (2.41); depressed = 5.92 (2.54) to 4.83 (2.56); anxious = 6.24 (2.53) to 4.97 (2.58); sad = 5.90 (2.69) to 4.64 (2.61); fear of future = 4.93 (2.77) to 4.06 (2.61); seeing life as a burden = 5.94 (2.66) to 4.97 (2.69); existential well-being = 4.22 (1.89) to 3.59 (1.81); personal existence = 4.62 (2.52) to 4.10 (2.41); achieving life goals = 5.34 (2.69) to 4.78 (2.64); life is worthwhile = 4.53 (2.47) to 4.04 (2.39); self-content = 4.76 (2.71) to 4.17 (2.51); closeness to people = 2.92 (2.49) to 2.14 (2.13); world is caring = 2.97 (2.22) to 2.23 (2.04); dignity = 4.41 (2.98) to 3.68 (2.68); support = 6.55 (2.34) to 6.12 (2.53); eating = 6.34 (2.61) to 6.17 (2.84); sex = 6.37 (3.03) to 6.08 (3.12); overall QOL = 6.81 (2.27) to 5.87 (2.53)
Ezat et al., 2014 [84]	General satisfaction aspect, feeling at peace and having a sense of meaning in life	QOL	N/A	Mean (SD) = 63.96 (17.41)
	Time spent with doctor; accessibility	N/A	Physical component; mental component	Mean (SD) physical component = 42.24 (7.91); mental component = 44.93 (6.84)

Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Fan et al., 2011 [48]	Diagnosis awareness (aware)	Physical functioning and emotional functioning	N/A	Mean (SD) physical functioning = 38.45 (22.95); emotional functioning = 61.05 (19.27)
Kim, 2014 [22]	Age (> 70), sex (male), living with parents, not using analgesics, less symptoms other than pain	Overall QOL	N/A	N/A
Kim et al., 2013 [49]	Aware of terminal status (aware); primary cancer site (colorectal, gastric), lower depressive symptoms	QOL	N/A	Positive improvement in median (interquartile range) score: awareness of terminal status (unaware vs. aware) 60 (46.3–73.8) vs. 50 (30–70); primary cancer site colorectal 50 (40–70); gastric 60 (50–70); hepatobiliary 60 (46.3–60); pancreas 50 (30–70); head and neck 35 (30–70); metastatic to lung (no vs. yes) 60 (40–70) vs. 50 (35–70)
Kristanti et al., 2017 [23]	Basic skills training for family caregivers (educational package: instructional and informational video as well as demonstrations by nurse educators), age, sex (female), caregivers age and experience	Global health status; functional scales (emotional, and social function), symptoms/single items (fatigue, pain, dyspnea, insomnia, appetite loss, constipation, financial)	N/A	Mean (SD) global health status = 40.27 (17.79) to 56.94 (18.05); functional scales: emotional function = 63.33 (30.21) to 79.44 (26.77); social function = 20.56 (25.40) to 35.56 (33.82); symptoms: fatigue = 68.33 (24.20) to 56.29 (28.12); pain = 72.22 (33.99) to 57.22 (34.35); dyspnea = 38.89 (39.22) to 12.22 (28.34); insomnia = 57.78 (66.67) to 35.56 (36.04); appetite loss = 60.00 (39.53) to 44.44 (36.40); constipation = 32.22 (38.63) 20.00 (34.57); financial = 78.89 (29.66) to 65.55 (33.31)
Lau et al., 2013 [9]	Sex (female), walking ability (more ambulant)	Global QOL by single-item scale; overall QOL	N/A	Mean (SD) global QOL by single item = 5.72 (1.84); overall QOL = 6.27 (1.26)

Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Lee et al., 2015 [34]	Patient grouping (nonproblematic group)	Global health status; symptoms: fatigue; nausea; pain; dyspnea; insomnia; appetite loss; constipation; emotional function; cognitive function	N/A	Median survival days (CI95%) global health status = 101 (83–120); symptoms: fatigue = 93 (74–103); nausea = 77 (69–88); pain = 84 (69–98); dyspnea = 75 (69–88); insomnia = 77 (69–90); appetite loss = 94 (82–110); constipation = 77 (69–91); emotional function = 77 (69–93); cognitive function = 80 (69–93)
Lee et al., 2014 [85]	Performa status, cancer-related symptoms	Physical functioning	N/A	N/A
Lee et al., 2013 [50]	Awareness of incurable cancer status (aware)	Overall quality of life; role functioning; emotional functioning; social functioning	Depression; financial difficulty	N/A
Li et al., 2014 [86]	Role functioning; financial impact, fatigue; depression and anxiety	N/A	Global health status	Mean (SD) global health status = 39.82 (30.20)
Lua et al., 2011 [43]	Attitudes, beliefs and perceptions towards CIMT effectiveness in health maintenance, need for wider promotion, focus more on well-being, physical symptoms (CIMT user)	Global health status	N/A	Mean (SD), median global health status (for CIMT user) = 6.6 (2.8), 7.0; (for CIMT non-user) = 6.4 (1.9), 6.0
Pokpalagon et al., 2012 [44]	Having PC (non-pharmacological care strategy) at four institutions (religious organization/NGOs)	Overall QOL; well-being and transcendent	N/A	N/A
Shahmoradi et al., 2012 [87]	Functional status home-based PC	N/A	QOL	Mean ± SD QOL score = 189.9 ± 51.7
Tang et al., 2016 [51]	Prognostic awareness (accurate)	N/A	QOL; self-perceived sense of burden to others, anxiety	Mean (SD) QOL = 93.49 (25.58) to 75.05 (26.34)
Tsai et al., 2012 [39]	Symptoms (weakness, pain, anorexia, nausea/vomiting, dysphagia, restless/heat, abdominal fullness, constipation, dry mouth, dizziness), education of complexities in fatigue plus psychosocial and spiritual care	Fatigue	N/A	N/A
Wang et al., 2016 [58]	The meaning subscale (spiritual well-being), faith subscale	Total FACT-G score	N/A	Mean (SD) total score QOL = 78.15 (18.12)

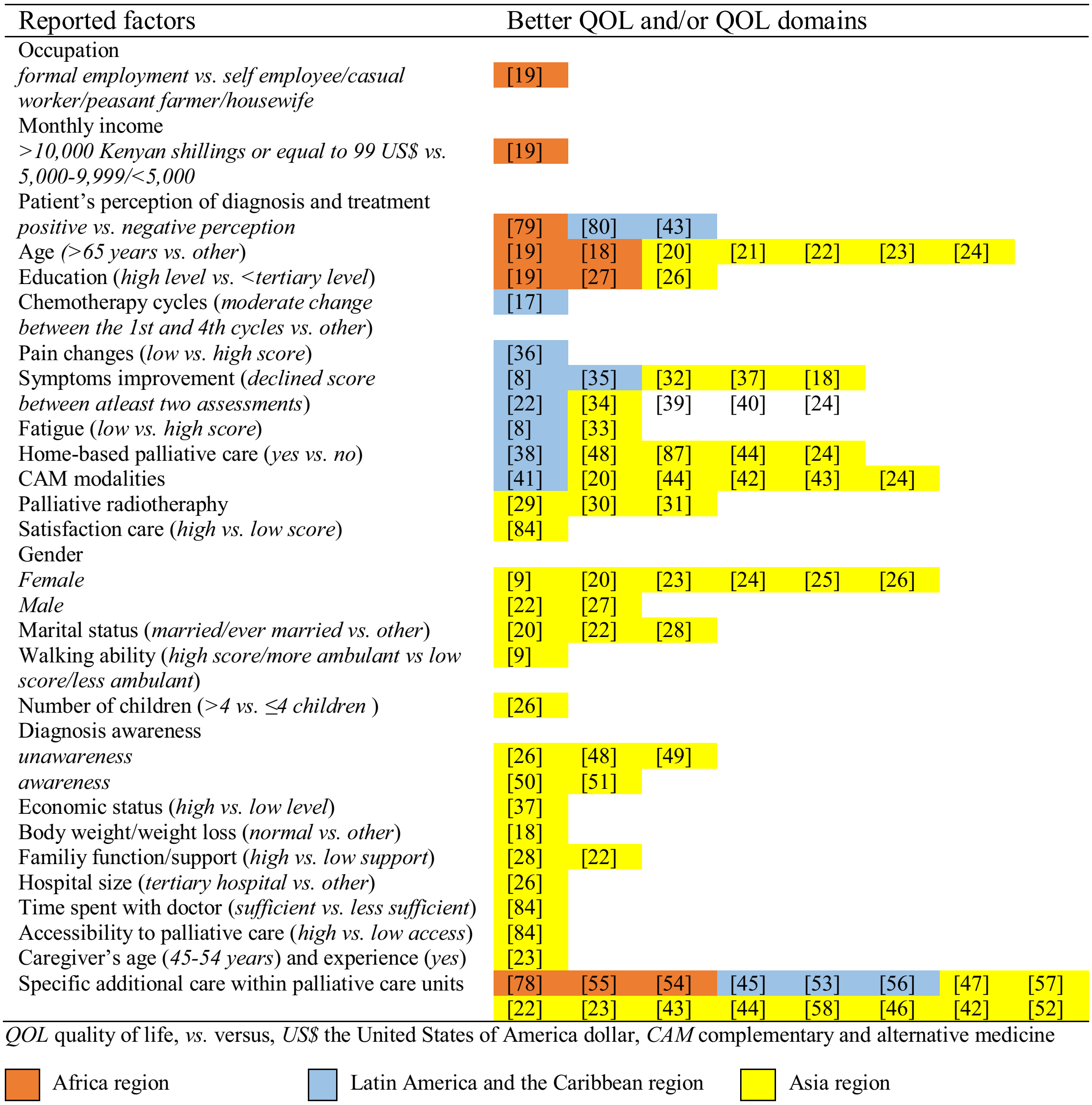
Table 2 (continued)

Author, year of publication	Factors studied	Better Outcome (QOL and/or QOL domains)	Poorer Outcome (QOL and/or QOL domains)	QOL and/or QOL domains Score
Wang et al., 2011 [40]	Each 13 symptoms (fatigue, difficulty remembering, disturbed sleep, pain, poor appetite, distress, sadness, dry mouth, numbness, short of breath, drowsiness, nausea, vomiting), the sum score of 13 symptoms	N/A	Total FACT-G score	Mean (SD) total score QOL = 62.2 ± 16.8
	Psychological symptoms (distress, sadness)	Total FACT-G score	N/A	Mean (SD) total score QOL (for distress) = 2.84 (2.59); (for sadness) = 2.61 (2,56)
Yan, 2006 [24]	Age, palliative home care patients, using traditional Chinese Medicine (TCM)	Total QOL score; sexual functioning score, psychological score; existential score	N/A	Mean (SD) total QOL score = 6.61 (0.85); sexual function = 7.23 (2.78); psychological function = 7.14 (1.18); existential function = 6.46 (1.49)
	Pain intensity	N/A	Overall QOL; physical score, sexual functioning score	N/A
Yoon et al., 2018 [46]	Spiritual well-being	Overall QOL	N/A	N/A

Only reported results with $P < 0.05$ are included

QOL quality of life, *N/A* not available, *PC* palliative care, *SD* standard deviation, *CIMT* complementary indigenous Malay therapies, *NGOs* non-governmental organizations, *IQR* interquartile range, *Gy* Gray (unit of inonizing radiation dose in the International System Units), *XRT* external radiotherapy, *ILB* intraluminal brachytherapy, *KPS* the Karnofsky performance status

Table 3 Factors associated with better quality of life in included studies by region

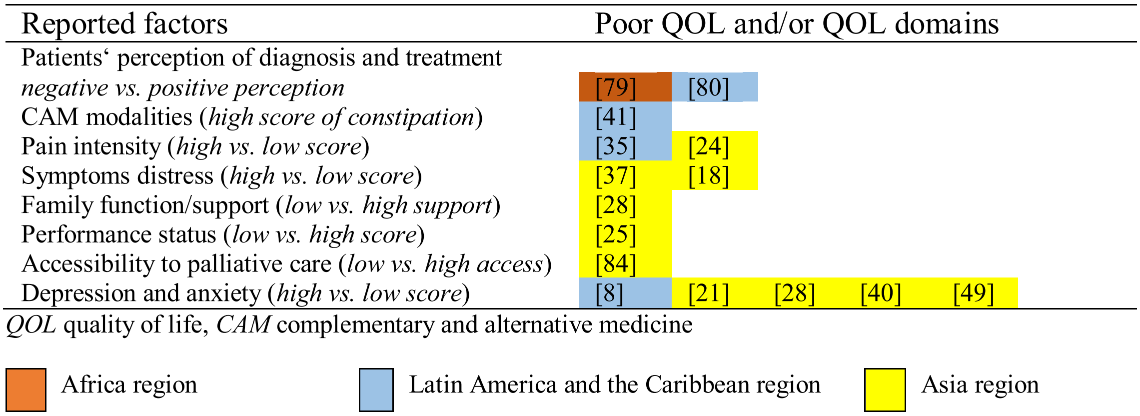


Reported factors	Better QOL and/or QOL domains							
Occupation								
formal employment vs. self employee/casual worker/peasant farmer/housewife	🟧 [19]							
Monthly income								
>10,000 Kenyan shillings or equal to 99 US$ vs. 5,000-9,999/<5,000	🟧 [19]							
Patient's perception of diagnosis and treatment								
positive vs. negative perception	🟧 [79]	🟦 [80]	🟦 [43]					
Age (*>65 years vs. other*)	🟧 [19]	🟧 [18]	🟨 [20]	🟨 [21]	🟨 [22]	🟨 [23]	🟨 [24]	
Education (*high level vs. <tertiary level*)	🟧 [19]	🟧 [27]	🟨 [26]					
Chemotherapy cycles (*moderate change between the 1st and 4th cycles vs. other*)	🟦 [17]							
Pain changes (*low vs. high score*)	🟦 [36]							
Symptoms improvement (*declined score between atleast two assessments*)	🟦 [8]	🟦 [35]	🟨 [32]	🟨 [37]	🟨 [18]			
	🟦 [22]	🟨 [34]	[39]	[40]	[24]			
Fatigue (*low vs. high score*)	🟦 [8]	🟨 [33]						
Home-based palliative care (*yes vs. no*)	🟦 [38]	🟨 [48]	🟨 [87]	🟨 [44]	🟨 [24]			
CAM modalities	🟦 [41]	🟨 [20]	🟨 [44]	🟨 [42]	🟨 [43]	🟨 [24]		
Palliative radiotheraphy	🟨 [29]	🟨 [30]	🟨 [31]					
Satisfaction care (*high vs. low score*)	🟨 [84]							
Gender								
Female	🟨 [9]	🟨 [20]	🟨 [23]	🟨 [24]	🟨 [25]	🟨 [26]		
Male	🟨 [22]	🟨 [27]						
Marital status (*married/ever married vs. other*)	🟨 [20]	🟨 [22]	🟨 [28]					
Walking ability (*high score/more ambulant vs low score/less ambulant*)	🟨 [9]							
Number of children (*>4 vs. ≤4 children*)	🟨 [26]							
Diagnosis awareness								
unawareness	🟨 [26]	🟨 [48]	🟨 [49]					
awareness	🟨 [50]	🟨 [51]						
Economic status (*high vs. low level*)	🟨 [37]							
Body weight/weight loss (*normal vs. other*)	🟨 [18]							
Familiy function/support (*high vs. low support*)	🟨 [28]	🟨 [22]						
Hospital size (*tertiary hospital vs. other*)	🟨 [26]							
Time spent with doctor (*sufficient vs. less sufficient*)	🟨 [84]							
Accessibility to palliative care (*high vs. low access*)	🟨 [84]							
Caregiver's age (*45-54 years*) and experience (*yes*)	🟨 [23]							
Specific additional care within palliative care units	🟧 [78]	🟧 [55]	🟧 [54]	🟦 [45]	🟦 [53]	🟦 [56]	🟨 [47]	🟨 [57]
	🟨 [22]	🟨 [23]	🟨 [43]	🟨 [44]	🟨 [58]	🟨 [46]	🟨 [42]	🟨 [52]

QOL quality of life, *vs.* versus, *US$* the United States of America dollar, *CAM* complementary and alternative medicine

🟧 Africa region 🟦 Latin America and the Caribbean region 🟨 Asia region

Table 4 Factors associated with poor quality of life in included studies by region



Reported factors	Poor QOL and/or QOL domains				
Patients' perception of diagnosis and treatment					
negative vs. positive perception	🟧 [79]	🟦 [80]			
CAM modalities (*high score of constipation*)	🟦 [41]				
Pain intensity (*high vs. low score*)	🟦 [35]	🟨 [24]			
Symptoms distress (*high vs. low score*)	🟨 [37]	🟨 [18]			
Family function/support (*low vs. high support*)	🟨 [28]				
Performance status (*low vs. high score*)	🟨 [25]				
Accessibility to palliative care (*low vs. high access*)	🟨 [84]				
Depression and anxiety (*high vs. low score*)	🟦 [8]	🟨 [21]	🟨 [28]	🟨 [40]	🟨 [49]

QOL quality of life, *CAM* complementary and alternative medicine

🟧 Africa region 🟦 Latin America and the Caribbean region 🟨 Asia region cancer patients, which tended to improve social well-being, was seen favorably compared to the single conventional course of radiation [29]. Moreover, a Brazilian study, which assessed QOL change in four chemotherapy cycles showed that QOL/physical functioning was improved in advanced lung cancer patients [17]. Furthermore, Avelino et al. stated that chemotherapy at baseline assessment might improve QOL (small changes), physical and cognitive functioning [17]. Similarly, Mehta et al. emphasized that despite limited sample size which made the comparison between schedules underpowered, their study indicated that a combination of external beam radiotherapy with intraluminal brachytherapy in advanced esophageal cancer resulted in prolonged symptom palliation and a better QOL compared with the external radiotherapy alone [30].

Complementary and alternative medicine (CAM)

Six studies assessed the use of CAM to treat cancer patients in PC in Asia and LAC region [20, 24, 41–44]. A study reported 16% of cancer patients received Chinese medicine, and 14% claimed to take alternative therapy in addition to the standard cancer treatment, but no association with QOL was found [20]. Two studies found the use of traditional medicines such as complementary indigenous Malay therapies [43], and Chinese medicine showed a better QOL/existential subscale, or physical symptoms score [24]. Chaiviboontham [42] stated that nearly 63% of cancer patients tended to use a combination of pharmacological and non-pharmacological PC strategies e.g. psychosocial care, mind–body intervention, and spiritual care; physical management; and traditional medicine, herbs, and diet management to treat their illness. This was associated with the effectiveness of PC, with improvements in symptoms relief and spiritual well-being [42]. Similarly, Pokpalagon et al. [44] reported non-pharmacological PC strategies based on the use of herbal medicines showed a better overall QOL and well-being compared to only standard medical therapy. In contrast, Alfano et al. [41] found few CAM modalities e.g. body-mind intervention and food supplements that negatively affected QOL domains. For example, cancer patients who used body-mind interventions demonstrated poorer cognitive function compared to non-users. However, the same patients also reported greater sexual enjoyment, and positive perception for the future [41].

Spirituality/religiosity

Despite limited number of studies assessing spirituality/religiosity, various religions were reported, e.g. Buddhism, Protestantism, Catholicism, Evangelic, and Hinduism. Two studies reported that some patients had no religious affiliation [45, 46]. Four Asian studies [42, 44, 46, 47] and one Brazilian study [45] stated that spirituality/religiosity was associated with better scores for QOL/QOL domains. For example, the Brazilian study indicated that around 95% of patients believed spirituality/religiosity helps them during stressful situations, supports them during cancer treatment, is a useful coping mechanism, and is an important aspect for assessment by health professionals [45]. One Thai study showed higher QOL in cancer patients who were exposed to non-pharmacological care strategies (social supports, mediation, or reading Dharma book/bible and making merit) in PC organized by religious institution compared to those who were treated in community/university hospitals. Reading Dharma book/bible and making merit as part of Buddhism practice was the most common non-pharmacological strategy used, because this tended to bring happiness, peaceful life, and strengthening of the ability to face obstacles/misfortunes. It provided with a better stress coping mechanism and a better QOL [44]. Similarly, Kandasamy et al. stated that spirituality/religiosity has been closely linked to PC in India and was an important part of Indian cancer patients' daily life, which acted as a coping stress mechanism, and could positively influence physical and psychological symptoms of distress [47]. A Korean study suggested that religion often provided comfort, a reason for living, a purpose in life, and harmony to cancer patients during their cancer treatments. Individual spiritual activities such as prayer, meditations, reading religious scriptures were beneficial for patients' QOL/spiritual well-being, and in close relation with better hope and positive mood [46].

Diagnosis awareness

Diagnosis awareness was assessed by five Asian studies [26, 48–51]. In general, the proportion of patients' awareness of their diagnosis was low, with a range from 17.5 to 50% [26, 48, 50], with only two studies showing a higher proportion [49, 51]. There are inconsistent reports if diagnosis awareness is associated with better QOL/QOL domains. For example, a South Korean study found a positive association between diagnosis awareness and QOL, role, emotional, and social functioning [50, 51]. Despite the positive association, Lee et al. emphasized that their result should be interpreted carefully [50]. In contrast, three studies reported opposite results [26, 48, 49]. Patients who were unaware of their diagnosis were more likely to have better physical and emotional functioning [48], and better overall QOL [26, 49] compared to those who knew their diagnosis. Fan et al. reported that the information non-disclosure gave a more hopeful outlook for patients, and increased the fighting spirit against the disease [48]. Cultural aspects were likely to play an important role for this non-disclosure. In some Asian cultures, a cancer diagnosis is a taboo concept, and patients often feel stigmatized and ashamed by their health condition; therefore, diagnosis unawareness could attribute to better physical and emotional functioning [48, 49].

Depression and anxiety

Five included studies showed that a high score for depression/anxiety is associated with poor QOL, physical well-being, emotional well-being, and functional well-being [8, 21, 28, 40, 49]. In our review, the proportion of advanced cancer patients feeling depressed and anxious ranged from 21.1 to 62%. This condition might decrease one's hope and peace, lead to increase of physical pain, risk of suicide, and poor QOL [21, 28]. Chan et al. stated that other psychological domains of QOL e.g. being afraid of the future, feeling sad, and feeling a burden to others might intertwine with depression and anxiety [21]. Similarly, Kim et al. emphasized that depression is strongly associated with hopelessness, which negatively influences physical and psychospiritual well-being, and the immune system [49].

Common factors across regions

Some factors were found only in one specific region, while some commonly appeared within two or even in all three regions (Tables 3, 4). For example, included studies from the African region mostly explored sociodemographic factors e.g. occupation, income, age, and education (Online Resource 5), whereas the LAC's studies provided information on factors in clinical settings and only one sociodemographic factor (patient's perception of diagnosis and treatment). The included studies from the Asian region contributed to various factors in both clinical setting and sociodemographic aspects. The only common factor shared by all regions was specific additional care within PCUs e.g. symptoms management on pain and fatigue, spirituality/religiosity, psychosocial counseling, basic skills training for family caregivers, or exposure to integrated care management [22, 23, 42–47, 52–58].

Discussion

This review indicates that in developing countries, cancer patients in PC who were older (> 65 years), married/ever married, had high educational level, used CAM, and practiced spiritual/religious activities were more likely to have higher scores in QOL/QOL domains. However, for patients with other characteristics e.g. younger patients, PCUs should be able to recognize and provide services that meet their needs [59]. Our review provides a broad perspective in terms of cancer types, geographical area, and factors that influence PC patients' QOL. One previously published review focused on similar QOL context, but was limited only to the Asian region, non-PC, and female breast cancer survivors [60]. Our findings are in line with this study that individual and cultural perspectives, such as the use of CAMs, and spiritual/religious practices were key factors for a better QOL in cancer patients.

Advanced cancer patients experience a range of symptoms for which standard medical treatments may not provide sufficient relief [61]. Consequently, patients seek and use CAM as addition to standard cancer care. Our review showed that CAM modalities positively influence cancer patients' QOL/QOL domains in PC. There are several possible explanations for this finding. First, in most developing countries standard cancer treatment options are limited, while CAM is available, accessible and affordable. One African study stated that most of the population in Africa lives in rural areas where standard healthcare services are limited [62]. This results in CAM being their primary source of healthcare. Second, the influence of cultural and historical factors is very important. Despite the well-established healthcare services in Singapore and South Korea, around 80% of their patients reported using CAM [63]. Moreover, most developing nations have their own traditional forms of healing stemming from their culture and history [64]. Last, as indicated by a British study, because of the failure of standard medical treatment or experiencing adverse effect from previous medical cancer treatment, patients are choosing CAM also in developed countries [65]. As demand for CAM increases worldwide [66], the safety and quality aspects remain an unaddressed issue [64]. CAM are considered as natural products and thus very safe, which is not necessarily true. Some CAMs might have a negative effect on patients and reduce the effectiveness of anticancer treatment [64]. Therefore, the WHO encourages CAM to be integrated and regulated by health service systems, particularly in PC, and evaluated with similar methods as standard treatment, such as clinical trials, to increase their quality and safety.

Having terminal illness is a highly depressing and anxiety-inducing condition. Our findings suggest that spirituality/religiosity positively affect cancer patients' ability to cope with this situation. This can be explained by several mechanisms e.g. encouraging healthy behaviors, giving social supports, providing a belief system, offering coping mechanism, and influencing neuroendocrine and neuroimmunology pathways [64, 67]. Spirituality/religiosity also provides social support, facilitating a faster adaptation to the stressors [67]. A previous review of nearly 300 studies worldwide assessing the association between spirituality/religiosity and anxiety reported that around 50% of studies on this topic showed an inverse correlation [67]. A meta-analysis found that spirituality/religiosity-based interventions in developed countries had a positive effect on anxiety, stress levels, decreased alcohol use and late onset of depression [68]. According to one American longitudinal study, spirituality/religiosity is considered cost-effective [69], and helps give meaning to patients' suffering and assists them in finding hope [70]. Therefore, recognizing spirituality/religiosity needs of cancer patients in PCUs by healthcare professionals is necessary.

Several individual characteristics such as age, gender, SES, and education are known to be linked to QOL domains as reported by previous studies from the USA [71], Turkey [72], and Asian countries [60]. However, there were some inconsistent findings, for example regarding diagnosis awareness. This inconsistency may be due to cultural differences across the regions. In many countries, disclosure of diagnosis and prognosis information of cancer patients is prohibited by the family or caregivers. This situation mostly happens because caregivers and/or health professionals assume that the disclosure of information on near death is detrimental to patients' psychological wellbeing. However, patients' acceptance following their diagnosis might positively influence their QOL. For example, traditional cultural values put a strong emphasis on concepts such as Buddhist and Confucian beliefs of enduring suffering [73]. Culture and ethnicity influences patients' perspectives and experiences toward health and illness; therefore, assessing QOL domains especially related to acceptance of disease status is highly recommended.

There are several similarities, but also differences in factors affecting QOL of cancer patients between developed and developing countries [7]. One main difference is that the evidence reported by studies from developed countries is considered more robust due to a better methodological approach. While most studies in developed countries are commonly conducted as RCTs [74, 75], the cross-sectional study design is often used in developing countries. Factors with a positive effect on QOL are similar between developed and developing countries, such as use of CAM and spirituality/religiosity, in addition to the standard cancer treatment. However, direct comparison of these factors between countries remains a major issue; therefore, to achieve standardization of various non-medical cancer treatments further research in this context is needed.

Establishing PC services and incorporating them in national cancer programs might be challenging for most developing countries. PC development requires four important pillars: policy, education, medication availability, and implementation [76]. However, weaknesses in the healthcare system of developing countries limits PC implementation. Therefore, the WHO is strongly advocating for locally adapted PC services in all nations and emphasizing that access to these services is an important part of universal healthcare coverage schemes [59]. This idea is supported by evidence that PC is cost-effective and can decrease inefficient spending in healthcare for inappropriate hospital admissions, long hospital stay, inappropriate and ineffective use of medicine and/or treatment [59, 77]. Despite some challenges, our review puts emphasis on the possibility of improving QOL of advanced cancer patients even in limited-resource settings.

Limitations

Over half of the articles had a low score in the quality assessment; therefore, the results should be carefully interpreted. The different types of QOL questionnaire in the included studies limit the comparability between studies. The included studies had various patient selection criteria, which might contribute to the inconsistency of some findings. Most studies had small sample size (< 300), and convenience samples, which makes the generalization of the results difficult.

Conclusion

In developing countries, cancer patient's sociodemographic characteristics (age, gender, marital status, and education) and cultural perspectives (the use of CAM, spirituality/religiosity) were key factors influencing QOL/QOL domains scores in PC. While CAM strategies and spiritual/religious practices were used and valued by cancer patients, its quality and safety aspects should be addressed with a proper biological assessment. Therefore, each country should recognize patients' needs with more PC research and implement locally adapted strategies. Our narrative review should be interpreted as a guideline for stakeholders which factors should be prioritized.

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Author contributions DG proposed the initial concept idea, conceived, and designed the systematic review protocol. DG, EJK, and RM designed search strategies. DG undertook the searches and retrieved articles. DG and LE performed the study selection, data extraction, and study quality assessment. DG wrote the first draft of the manuscript. All authors discussed, advised and revised the manuscript. All authors read and accepted the final version.

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Data availability The data and material of this systematic review are available to the public upon request.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethics approval This study reported only already published data. We had no direct access to the original data used in the included studies for the review. Therefore, no ethical approval was needed.

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Publication 2

Contribution as an author:

I have contributed to the conception and design of the work, formulation of the research questions, study questionnaire development (including a permission to use the Indonesian version of the EORTC QLQ-C15-PAL from the EORTC Quality of Life Group), ethical clearance processes, data collection (including one-day meeting with research assistants to reach a standard knowledge and technical aspects i.e., data collection procedures, how to use and address the study questionnaires, and monitoring the data collection), data dictionary development, data management, results interpretation, and wrote the manuscript. Also, I was responsible for the whole submission process until the manuscript was published.

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ORIGINAL RESEARCH

Quality of Life Assessment and Pain Severity in Breast Cancer Patients Prior to Palliative Oncology Treatment in Indonesia: A Cross-Sectional Study

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Purpose: Studies assessing quality of life (QOL) in palliative care settings are still scarce. We assessed the QOL score and pain severity in advanced breast cancer patients at the National Cancer Hospital in Indonesia and associations between QOL domains with QOL and pain scores.

Materials and Methods: A total of 160 patients who met the study inclusion criteria (female, >18 years old, diagnosed with stage III or IV breast cancer) answered the European Organization for Research and Treatment of Cancer QOL questionnaire (EORTC QLQ-C15-PAL) and the visual analogue scale (VAS) tool for pain severity, prior to palliative oncology treatment. Additionally, several sociodemographic and clinical characteristics were collected. Linear regression models, adjusted for age, the Karnofsky Performance Status (KPS) score, and specific QOL domains were used to explore the associations between the global QOL and VAS scores with the different QOL domains.

Results: The patients had a mean age of 50 years (range: 29–76). The overall score for QOL and score for VAS was (mean ± SD) 78.02 ± 15.34 and 2.1 ± 2.4, respectively. The analysis demonstrated that the domains of emotional functioning (effect estimate: 0.25; 95% CI: 0.14 to 0.37), fatigue (−0.21; −0.33 to −0.09), pain (−0.13; −0.25 to −0.01), insomnia (−0.25; −0.37 to −0.13), and appetite loss (−0.13; −0.25 to −0.008) were associated with the QOL score. Only the KPS score (−0.28; −0.46 to −0.11) was associated with the VAS score.

Conclusion: Our study showed high QOL and low VAS scores in advanced breast cancer patients prior to palliative oncology treatment. Several QOL domains (emotional functioning, fatigue, pain, insomnia, and appetite loss) were associated with QOL and the KPS was associated with the pain score. Therefore, these specific QOL domains should be given priority in improving QOL in this patient group.

Keywords: health-related quality of life, advance breast cancer, pain severity, EORTC QLQ-C15-PAL

Introduction

Breast cancer remains a major public health problem around the world. Approximately 2.2 million women worldwide develop this disease, and breast cancer is the most common cancer entity.[1] In Indonesia, it was estimated that in 2020 65,858 incidents of breast cancer cases and 22,430 annual deaths due to breast cancer occurred.[2] Advanced breast cancer patients often experience long-term chemotherapy or radiotherapy treatment and accumulation of psychological distress, chronic pain, and fatigue, which leads to impaired quality of life (QOL).[3–5]

QOL is a multidimensional concept that considers patients' subjective assessment of their situation at a specific time.[6] Despite its subjective aspect, QOL is

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considered valid, reliable, and responsive to capturing important clinical changes.[7,8] Moreover, QOL is an important patient-reported outcome that provides insight into patient's disease burden,[9,10] helpful in patient empowerment, and useful in the interpretation of clinical outcomes and treatment decision-making.[9]

Pain is one of the most common reported symptoms in cancer patients and occurs as part of the disease process or a side effect of cancer treatment. It represents a problem for most breast cancer patients and negatively affects the QOL.[6,7] A systematic review and meta-analysis, which assessed pain prevalence of adult cancer patients globally, stated that pain is prevalent in 39.3% of cases after curative treatment, 55.0% during cancer treatment, and 66.4% in advanced disease stages.[8] It is important to assess pain, as untreated chronic pain often worsens other QOL aspects (eg fatigue, nausea, constipation, sleep disturbances, and depression). Symptom control is an effective way to improve QOL of all cancer patients, but it is mostly important for advanced cancer patients who no longer respond well to curative or life-prolonging treatments.[11,12]

Despite growing evidence regarding the positive impact of QOL assessment and pain severity in advanced cancer, most QOL research was conducted in patients from developed countries, which have different needs and characteristics compared to patients from developing countries.[9] Moreover, studies showed that scores of QOL/QOL domains varied between countries[14–16] and there is a need for further research in patient-reported outcomes, such as QOL and pain severity, when planning patients' individual cancer management plans. Therefore, this study aims to assess QOL score and pain severity in advanced breast cancer patients prior to palliative oncology treatment at the National Cancer Hospital in Indonesia and identify which QOL domains (eg functional and symptom scales) are associated with the QOL score and pain severity.

Materials and Methods

Study Population

Patients at the oncology unit of the "Dharmais" cancer hospital in Jakarta, Indonesia were invited to participate in this cross-sectional study between January and February 2020. To enter the study, patients had to meet the study inclusion criteria: female; aged > 18 years; diagnosed with advanced breast cancer; had no difficulty in communicating during the data collection without the help of a caregiver; and were scheduled to start palliative oncology treatment. Advanced breast cancer was defined by the American Joint Committee on Cancer as stage III or IV breast cancer[10] and where no further curative treatment options were planned.[17] The primary palliative oncology treatments were chemotherapy and hormonal therapy, while radiotherapy and surgery were used if required to reduce symptoms, but not for curative purposes.[11] Patients with psychological disorders were excluded from the study.

The data collection was conducted following the admissions of patients to the oncology unit's nursing station before their consultation appointment with the oncologist. After the consultation, patients were referred to receive further palliative oncology treatment. While we did not have direct access to medical records, the hospital nurses facilitated the patients' screening process for potential study inclusion. We explained the purposes of the study to the invited participants before starting the interview. If the individual refused to participate, we documented the reasons for declining participation. All participants provided written informed consent that was in line with the Declaration of Helsinki.[18] The Ethics Committee of the "Dharmais" Cancer Hospital approved the study protocol (136/KEPK/VII/2019).

Study Instruments

Outcome variables (QOL score and pain severity) and QOL domains (physical and emotional functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, and constipation) were self-reported by patients.[19] For assessing the global QOL and QOL domains, the Indonesian version of the EORTC Quality of Life Questionnaire-Core 15-Palliative Care (EORTC QLQ-C15-PAL) was used, with the permission from the EORTC Quality of Life Group. The EORTC QLQ-C15 PAL is a 15-item validated and reliable tool for QOL assessment.[20] It is a short version of the EORTC QLQ-C30 core questionnaire,[21] of which the Indonesian version was validated.[22] The EORTC QLQ-C15-PAL consists of one global QOL item (question 15), in addition to several functional and symptom scales. The functional scales comprise questions regarding physical functioning (questions 1–3) and emotional functioning (questions 13 and 14). The symptom questions consist of a fatigue scale (questions 7 and 11), a pain scale (questions 5 and 12), and single items for the nausea and vomiting scale (question 9), dyspnea (question 4), insomnia (question 6), appetite loss (question 8), and constipation (question 10). For questions 1–

14, patients graded their response using a 4-point Likert scale: 1) not at all, 2) a little, 3) quite a bit, and 4) very much. For question 15, which assessed global QOL, a 7-point numerical scale with a score of 1 (very poor overall QOL) to 7 (excellent overall QOL) was used. All QOL/QOL domain responses were related to how the patient was feeling during the past week before the hospital consultation.

Pain severity was assessed using the visual analogue scale (VAS) method on a 0 (no pain) to 10 (worst pain) scale. The VAS provides responses that are reliable, valid, and mostly preferred by patients.[12] The VAS score represents the current pain severity status of patients during data collection.

We also collected sociodemographic characteristics, including age, place of residence, education, marital status, ethnic group, religion, and clinical characteristics (body mass index (BMI), the Karnofsky Performance Status (KPS), metastasis status, and history of cancer treatments (surgery, radiation, and chemotherapy)). The KPS assesses the functional capacity of patients related to daily activities on a scale from 0 to 100, with 0% (describing death) to 100% (representing normal activity).[13]

Statistical Analysis

For continuous sociodemographic and clinical data, results were expressed as mean and standard deviation (SD) or interquartile range (IQR) and median, depending on data distribution, while categorical variables were described with frequencies and percentages. Normal distribution was tested using a histogram plot. The scoring of the EORTC QLQ-C15-PAL domains was performed according to the EORTC QLQ-C30 Scoring Manual.[14] The scores for the EORTC QLQ-C15-PAL abbreviated scales (physical functioning, emotional functioning, nausea and vomiting, and fatigue) were estimated using the addendum to the EORTC QLQ-C30 Scoring Manual: Scoring of the EORTC QLQ-C15-PAL.[15] The EORTC QLQ-C15-PAL scoring principle was to calculate the mean values for all the items (the raw score), which was then linearly transformed to yield scores from 0 to 100. While a high score for the global QOL or the functional scales shows a better QOL or level of functioning, a high VAS score describes an unfavourable level of experienced pain. All items of the EORTC QLQ-C15-PAL and VAS are described as means (SDs).

The nonparametric Wilcoxon-Mann–Whitney and Kruskal–Wallis tests were used to assess the difference in several sociodemographic and clinical variables (eg BMI, place of residence, education, marital status, and age groups) on QOL/QOL domain scores. The Spearman rank correlation assessed the correlation between QOL score and specific QOL domains.

Linear regression models were used to investigate which QOL domains were associated with the global QOL item and the VAS score. First, the linear regression model was used to assess the association between global QOL and separately for each of the specific QOL domains (eg physical and emotional functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, and constipation) adjusted for age and the KPS score (Model I). Second, the association between the global QOL and the different QOL domain scores was examined, adjusting for all specific QOL domains and additionally for age and the KPS score (Model II). We used the same two-step analysis approach for the VAS score. We standardized all the regression coefficients and tested for multicollinearity in the multivariable analysis to explore the degree of correlation between independent variables included in the models. A recommendation of the variance inflation factors greater than 10 was used for identifying potential multicollinearity.[25] Data were analysed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Of 330 eligible advanced breast cancer patients approached, 160 patients completed the questionnaire and were included in the analysis. Each assessment took approximately 12 minutes per patient. The most common reasons for declining to participate were refusal to be interviewed (n = 31) and being too weak to answer the questionnaire (n = 24) (Figure 1).

In this study, the mean age was 50 years (range: 29–76), 72.5% of patients lived in urban areas, 71.8% had a low educational level, and 81.9% were married (Table 1). While the majority reported having received previous breast cancer treatments (surgery (96.9%) and/or chemotherapy (63.1%)), only 37.5% of patients had experienced radiation therapy. The mean KPS score was 80.7 ± 6.8, and on average, patients were overweight with a BMI of 25.9 ± 4.7 kg/m^2 (Table 1).

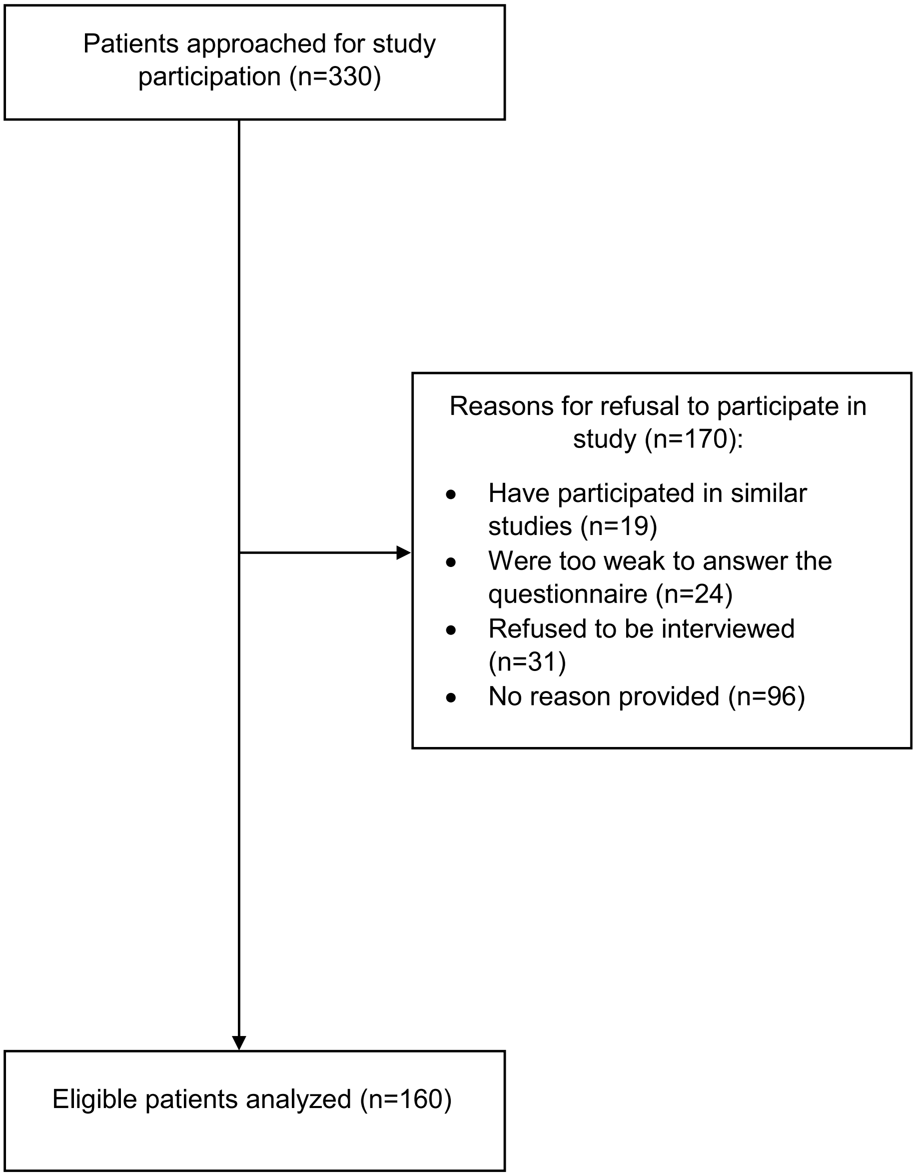

Figure 1 Flowchart of the study participants.

Quality of Life Assessment

The EORTC QLQ-C15-PAL mean scores for global QOL (78.02 ± 15.34), physical and emotional functioning were high, at 75 or above (Table 2). The score of most symptom scales in our study were reportedly good (range: 3.33 ± 11.79 to 8.54 ± 23.93), which describes that breast cancer patients had better symptoms experience. However, for fatigue, pain, and insomnia, the score was reportedly worse (range: 17.50 ± 33.11 to 24.01 ± 27.47 (Table 2). There were no differences in the QOL/QOL domain scores of advanced breast cancer across most sociodemographic and clinical characteristics (eg age groups, BMI with a cut-off point 25 kg/m^2, place of residence, education, and marital status) (Supplement Table 1). As expected, physical and emotional functioning (functional scales) was positively correlated with the QOL score and all symptom scales were negatively correlated with the QOL score (Supplement Table 2).

In a linear regression Model I, most of the EORTC QLQ-C15-PAL domains, except dyspnea, were associated with the global QOL score after adjustment for age and the KPS score (Table 3). However, in Model II, only some of the EORTC QLQ-C15-PAL domains remained associated with the global QOL score. A positive association was

Table 1 Sociodemographic Characteristics of 160 Advanced Breast Cancer Patients

Characteristics	N (%) or Mean ± SD
Age (years)[a]; range	50.2±8.3; 29–76
Body Mass Index, kg/m^2 [a]	25.9±4.7
Systolic Blood Pressure, mmHg[a]	128.8±16.6
Diastolic Blood Pressure, mmHg[a]	80.6±9.9
Pain severity (VAS)[a]	2.1±2.4
Place of residence	
Rural	44 (27.5)
Urban	116 (72.5)
Educational level	
Low (never/primary/junior/senior high school)	115 (71.8)
High (vocational/under-/postgraduate degree)	45 (28.2)
Marital status	
Single/separated/widow/widower	29 (18.1)
Married	131 (81.9)
Ethnic group	
Javanese	58 (36.3)
Sundanese	47 (29.4)
Batak	5 (3.1)
Betawi	25 (15.6)
Minangkabau	6 (3.7)
Bantenese	1 (0.6)
Malay	7 (4.4)
Others	11 (6.9)
Religion	
Islam	138 (86.2)
Protestant	14 (8.8)
Catholic	7 (4.4)
Buddhist	1 (0.6)
Karnofsky Performance Status, %[a]	80.68±6.8
History of surgery	
Yes	155 (96.9)
No	5 (3.1)
Did not know	0 (0.0)
History of radiation	
Yes	60 (37.5)
No	97 (60.6)
Did not know	3 (1.9)
History of chemotherapy	
Yes	101 (63.1)
No	55 (34.4)
Did not know	4 (2.5)
Metastasis status	
Yes	33 (20.6)
No/did not know	127 (79.4)
Pain therapy	
Yes	9 (5.6)
No/did not know	151 (94.4)

(Continued)

Table 1 (Continued).

Note: [a]Mean ± standard deviation.
Abbreviation: VAS, visual analogue scale.

Table 2 Mean Quality of Life, Functional Scale, and Symptom Scale Scores

EORTC QLQ-C15-PAL	Mean ± SD
Global quality of life (15)	78.02±15.34
Functional scales	
Physical functioning (1–3)	89.88±12.32
Emotional functioning (13, 14)	81.29±20.67
Symptom scales	
Fatigue (7, 11)	22.76±28.41
Nausea and vomiting (9)	4.27±15.21
Pain (5, 12)	24.01±27.47
Dyspnea (4)	3.33±11.79
Insomnia (6)	17.50±33.11
Appetite loss (8)	8.54±23.93
Constipation (10)	4.16±17.13

Abbreviations: EORTC QLQ-C15-PAL, the European Organization Research and Treatment for Cancer Quality of Life Questionnaire Core 15 items for palliative care; SD, standard deviation; VAS, visual analogue scale.

found for emotional functioning (effect estimate: 0.25; 95% CI: 0.14 to 0.37) and a negative association was found for fatigue (−0.21; −0.33 to −0.09), pain (−0.13; −0.25 to −0.01), insomnia (−0.25; −0.37 to −0.13), and appetite loss (−0.13; −0.25 to −0.008) (Table 3).

Pain Severity (VAS)

The mean score for VAS was low (2.1 ± 2.4), which indicated reasonable control of pain (Table 1). In Model I, most of the domains, except nausea and dyspnea, were associated with the VAS score. However, only the KPS score remained negatively associated with the VAS score in Model II (effect estimate: −0.28; 95% CI: −0.46 to −0.11) (Table 4).

Discussion

This study assessed the QOL score and pain severity in Indonesian advanced breast cancer patients prior to palliative oncology treatment. Several QOL domains (emotional functioning, fatigue, pain, insomnia, and appetite loss) were associated with the global QOL score. Only the KPS score

Table 3 Linear Regression Analyses of Associations for Quality of Life Score

EORTC QLQ-C15-PAL	**Model 1**		**Model 2**	
	Effect Estimate (95% CI)	**p-value**	**Effect Estimate (95% CI)**	**p-value**
Functional scales				
Physical functioning	0.30 (0.15 to 0.46)	**0.0001**	0.09 (−0.03 to 0.22)	0.15
Emotional functioning	0.40 (0.27 to 0.53)	**<0.0001**	0.25 (0.14 to 0.37)	**<0.0001**
Symptom scales				
Fatigue	−0.43 (−0.56 to −0.30)	**<0.0001**	−0.21 (−0.33 to −0.09)	**0.0006**
Nausea and vomiting	−0.26 (−0.40 to −0.12)	**0.0003**	−0.08 (−0.21 to 0.04)	0.20
Pain	−0.33 (−0.46 to −0.19)	**<0.0001**	−0.13 (−0.25 to −0.01)	**0.02**
Dyspnea	−0.05 (−0.19 to 0.08)	0.42	–	–
Insomnia	−0.47 (−0.61 to −0.34)	**<0.0001**	−0.25 (−0.37 to −0.13)	**<0.0001**
Appetite loss	−0.34 (−0.49 to −0.20)	**<0.0001**	−0.13 (−0.25 to −0.008)	**0.03**
Constipation	−0.16 (−0.31 to −0.01)	**0.02**	−0.01 (−0.13 to 0.10)	0.81

Notes: Model 1 is age and Karnofsky Performance Status score adjusted; Model 2 is adjusted for variables from Model 1, in addition to the other domains from the EORTC QLQ-C15-PAL questionnaire; All reported effect estimates have been standardized. Statistical significance of bold values when p<0.05.
Abbreviation: EORTC QLQ-C15-PAL, the European Organization Research and Treatment for Cancer Quality of Life Questionnaire Core 15 items for palliative care.

Table 4 Linear Regression Analyses of Associations for Pain Severity (VAS)

Variables/ EORTC QLQ-C15-PAL	**Model 1**		**Model 2**	
	Effect Estimate (95% CI)	**p-value**	**Effect Estimate (95% CI)**	**p-value**
Age	0.04 (−0.10 to 0.20)	0.53	–	–
KPS score	−0.39 (−0.54 to −0.25)	**< 0.0001**	−0.28 (−0.46 to −0.11)	**0.001**
Emotional functioning	−0.29 (−0.44 to −0.14)	**0.0002**	0.15 (−0.31 to 0.01)	0.06
Physical functioning	−0.25 (−0.40 to −0.09)	**0.001**	−0.003 (−0.17 to 0.17)	0.97
Constipation	0.14 (−0.006 to 0.30)	0.06	–	–
Appetite	0.07 (−0.08 to 0.23)	0.35	–	–
Insomnia	0.28 (0.13 to 0.43)	**0.0002**	0.06 (−0.11 to 0.24)	0.47
Nausea	0.03 (−0.11 to 0.19)	0.61	–	–
Dyspnea	0.06 (−0.09 to 0.21)	0.43	–	–
Fatigue	0.21 (0.06 to 0.36)	**0.006**	0.007 (−0.16 to 0.18)	0.93
Quality of life	−0.34 (−0.49 to −0.19)	**< 0.0001**	−0.08 (−0.30 to 0.13)	0.43

Notes: Model 1 designates the effect estimates from univariable analyses of the single domain variable, age and KPS; Model 2 was adjusted for all significant variables from Model 1; All reported effect estimates have been standardized. Statistical significance of bold values when p<0.05.
Abbreviations: CI, confidence interval; EORTC QLQ-C15-PAL, the European Organization Research and Treatment for Cancer Quality of Life Questionnaire Core 15 items for palliative care; KPS, Karnofsky Performance Status; VAS, visual analogue scale.

was associated with the VAS score among the assessed variables. Interestingly, our findings showed that the QOL was higher and VAS score was lower in this study than in previous studies in a similar context.

Quality of Life Among Cancer Patients

In general, QOL and QOL domain scores in advanced breast cancer individuals are expectedly poor.[26] Our study supported this finding, but our results showed a higher score of global QOL and QOL domains as compared to previous studies in breast cancer patients.[16,17] There are several possible explanations for our findings. The first key component is the methodological aspect. In this study, some participants who were too weak to answer the questionnaire refused to participate, resulting in missing information from those who were in special need of particular treatments and contributing to non-response bias.[18] The second explanation for the high score of QOL is possible unawareness of the disease's prognosis as per discussion with oncologists in the hospital (personal communication). As our study subjects were patients who were referred to the palliative oncology department, the planned treatment could be assumed for a curative purpose, instead of palliative, resulting in better scores for QOL/QOL domains.[13] The palliative situation was possibly not directly communicated or not clearly explained to patients due to fears of caregivers and relatives that patients may lose hope.[19] The inadequate ratio between doctors and patients in most developing countries often leads to insufficient consultation time[13] and poor patient-doctor communication,[20] resulting in unclear information on the accurate prognosis of the patient.[21] However, communicating and confirming the accurate prognosis is important for advanced cancer patients as it relates to cancer treatment plans, matching with their individual/cultural preferences and values.[13] Consequently, this communication process is highly appreciated and valued by patients, since including their perspective in the cancer treatment plan provides them with a sense of dignity and confidence.

Last, cultural aspects play a key role in the QOL of advanced cancer patients. For example, caring for a family member is part of Indonesian and Asian culture. When a household member is diagnosed with cancer, other family members will provide support, take care of the patient, and act as caregivers.[22,23] Caring for a family member with cancer is considered an obligation and responsibility in Asian culture.[24] Consequently, strong family bonds and good communication between patients and caregivers develop during the disease process and its treatment.[23,25] This social and psychological support positively influences patients' QOL/QOL domains.[23,26] In contrast, patients who were unsupported by family members were reported to have a high score of anxiety/depression and poor QOL.[27] Also, spirituality and religiosity are key components of Indonesian culture and influence the motivation to care for cancer patients.[27] For instance, studies reported that spiritual and religious practices in Indonesia and most developing countries acted as a positive factor for providing comfort and support for a sick family member[26,28] and positively affected cancer patients' ability to cope.[29] Since most of our patients were religious individuals (around 90%), this aspect adds to the explanation of our findings. As various individual and cultural factors influence the QOL/QOL domains of advanced cancer patients, it is necessary to acknowledge the perspectives of patients and caregivers during cancer treatment management.

Pain Severity

Pain is prevalent among advanced cancer patients, but our study sample surprisingly had lower VAS scores or better pain experiences as compared to previous studies.[30–32] Hospital physicians confirmed that pain was rarely reported in the setting (personal communication, Supplement Table 3). Possible explanations could be several non-pharmacological reasons, such as psychological, sociocultural, behavioral, and affective aspects.[32] Evidence indicates that the role of psychological factors and behavior (eg coping and emotional distress) should be considered in both non-cancer- and cancer-related pain.[33] Consequently, the importance of psychological and behavioral treatments was emphasized as non-pharmacologic options that are recommended, together with pharmacologic interventions, to achieve effective pain management. For example, an intervention targeting the development of adaptive coping strategies may enhance a patient's feeling of confidence in managing his or her pain, which in turn may be associated with a reduction in pain intensity or severity and with a reduction in emotional distress and consequent increase in QOL.[34] Therefore, it is important to recognize the complex and multidimensional nature of patients' experiences with cancer-related pain and also their response to this pain.

Our findings did not show an influence of sociodemographic and clinical characteristics on QOL and pain severity. This was possibly due to a homogeneous patient group, in addition to missing those patients in poor condition, and the convenience sampling method used. However, previous evidence has indicated that QOL is influenced by various individual aspects (eg age, sex, educational level, marital status, number of children, living situation, and diagnoses).[16,17,32] Moreover, several cultural aspects (eg spirituality/religiosity) play an important role in personal motivation, symptom amplification, and value preferences.[35] Consequently, patients' symptoms and functional status, general health perception, and global QOL can presumably be influenced by all these factors.[6] As shown by our models, several symptom scales of QOL domains affect advanced breast cancer patients' QOL. Similarly, a Bahraini study showed that the most distressing symptoms on the symptom scales were fatigue, sleep disturbance, and pain which were negatively associated with QOL score.[17] Therefore, we believe if physicians give more attention to cancer related symptoms such as fatigue, pain, and insomnia during patients' counseling in this setting, QOL improvement can be achieved in this patients' group.

The QOL of advanced cancer patients is a complex situation, incorporating dynamic multidimensional circumstances and requires appropriate strategies, such as comprehensive oncology services or palliative care, which will maintain/ increase QOL and facilitate efficient allocation of medical resources. It is evident that providing PC to patients regardless of their cancer stage is highly recommended.[36] A systematic review indicated that advanced cancer patients who received PC had better QOL and symptoms than those in conventional cancer treatment.[30] However, our study assessed QOL and pain severity in advanced breast cancer patients prior to palliative oncology treatment; therefore, an analysis of follow-up data is needed to explore this hypothesis.

Strengths and Limitations

Our study contributes to a better understanding of QOL assessment and pain severity in Indonesia prior to palliative oncology treatment at the National Cancer Hospital where standardized palliative oncology had been implemented and practiced. The questionnaire was standardized and thus comparable to a large number of studies conducted elsewhere in the world.

There are also several limitations. The self-reported approach has constraints, such as the information about the metastatic disease might have introduced a reporting bias since patients sometimes neglect unwanted information. The convenience sampling might result in an underpowered analysis, which explains the absence of differences in sub-group analyses (eg urban/rural or married/single). We were unable to obtain detailed medical records. However, since hospital nurses facilitated the screening process for patients' eligibility criteria, we did assume considerable reliability of the medical information. Another limitation is the low participation of patients in a poor condition, leading to under-representation of lower QOL and higher VAS scores. This is a common problem in QOL and pain studies. In spite of that, our study was proficient enough to describe QOL assessment and pain severity within the population composition as described.

Conclusion

Our study, which assessed the QOL and pain severity of advanced breast cancer patients` cohort before palliative oncology treatment, showed better QOL and VAS scores in Indonesia compared to previous studies. Also, our findings indicated that QOL score were associated with several QOL domains (emotional functioning, fatigue, pain, insomnia, and appetite loss) of the EORTC QLQ-C15-PAL, while the VAS score was associated with KPS. Therefore, these specific QOL domains should be given proper attention by treating oncologists before palliative oncology treatment in this patient group.

Abbreviations

BMI, body mass index; EORTC, European Organization for Research and Treatment of Cancer; QLQ-C15-PAL, validated quality of life questionnaire for advanced cancer stage; IQR, interquartile range; KPS, Karnofsky Performance Status; QOL, quality of life; SD, standard deviation; VAS, visual analogue scale.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the "Dharmais" Cancer Hospital (study protocol number 136/ KEPK/VII/2019) and in accordance with the Declaration of Helsinki. All patients signed the written informed consent before participating in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the revision to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interest.

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Declarations of independence

(1) I declare that I have not completed or initiated a doctorate procedure at any other universities.

(2) I declare that all information given is accurate and complete. The thesis has not been used previously at this or any other university in order to achieve an academic degree.

(3) I declare under oath that this thesis is my own work entirely and has been written without any help from other people. I complied with all regulation of good scientific practice and I used only the sources mentioned and included all the citations correctly both in word or content.

Halle (Saale), Dwi Gayatri

Declarations of previous dissertation attempt

I declare that this work is the first attempt of writing a dissertation. Also, I declare that this work is exclusively submitted as a dissertation for the Medical Faculty of Martin Luther University Halle-Wittenberg.

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