

Quality of Life and Morphine Dose in Cervical Cancer Patients with Chronic Pain

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Abstract

Introduction: Cervical cancer in Indonesia is the second leading cancer in women. Improved management has increased the life expectancy of patients, but will be followed by various experiences that can be unpleasant such as pain. Pain is one of the main problems that reduce the quality of life of cancer patients. Pain is negatively associated with quality of life and has implications for all dimensions of quality of life. It is becoming increasingly important to evaluate the quality of life of patients with chronic diseases and the effects of treatment, particularly in the field of oncology. Reliable opioid use is crucial in cancer pain patients. Morphine is still the main choice for several reasons such as familiarity, availability and cost compared to the efficacy of other drugs. **Aim and Objective:** This study aims to examine the relationship between quality of life, as assessed by the EORTC QLQ-C30 questionnaire, and daily morphine dose in cervical cancer patients with chronic pain. **Materials and Methods:** A cross-sectional study with 42 subjects of cervical cancer patients with chronic pain. Subjects were interviewed and asked to complete the EORTC QLQ-C30 questionnaire and daily morphine dose was reviewed from medical records. **Results and Conclusion:** In 42 subjects, the age of the subjects was 27-63 years old with cancer stages 3 and 4. The average daily morphine dose was 50.24 mg / day. In the analysis of quality of life with morphine dose, meaning was found on the global health status scale ($r = -0.467$, $p = 0.002$), pain symptom scale ($r = 0.363$, $p = 0.018$), and constipation symptom scale ($r = 0.418$, $p = 0.006$). For other scales, no significant relationship was found. Quality of life was associated with daily morphine dose on global health status, pain symptoms, and constipation symptoms scales. However, no relationship was found on other scales.

Keywords: Cervical Cancer, Chronic Pain, EORTC QLQ-C30, Morphine, Quality of Life

1. Introduction

Cervical cancer is the second most common cancer in women in Indonesia, with over 30.000 new cases annually (1). As management options continue to improve, patients' life expectancy is increasing. However, this is often accompanied by an increase in symptoms and a decrease in quality of life (2). Quality of life for cancer patients describes their physical, psychological, and social functions related to daily activities and roles, and has a significant impact on their overall well-being (3). The EORTC QLQ-C30 questionnaire is a widely used tool for assessing quality of life in cancer patients, including in Asia (4–6). In Indonesia, research has been conducted to validate the questionnaire's reliability (7). Evaluating the quality of life of patients with chronic diseases, especially in oncology, is increasingly important to understand the effects of treatment and improve patient services and compliance (8).

Pain is a major problem that significantly reduces the quality of life for cancer patients. A reported 52.2% of patients receiving cancer treatment and 74.8% of patients undergoing treatment for metastasis experienced pain. A review found that around 46% of patients with cancer pain experienced moderate

to severe pain (9,10). Pain has a negative impact on all aspects of quality of life. Inadequate pain control in cancer patients has been a persistent issue, resulting in numerous studies on pain control and strategies to improve it. Improving pain control is crucial in reducing the burden associated with inadequate pain control and the resulting decrease in quality of life (11,12).

The World Health Organization (WHO) has introduced the analgesic step ladder principle for managing pain, both acute and chronic. A new step ladder model that offers multimodal analgesia has been introduced by Anekar & Cascella (13). Opioids are included in this analgesic ladder and can be an option for moderate to severe pain in acute and chronic pain patients.

Reliable opioid use is crucial in managing pain for cancer patients, yet there is limited data available to support clinical practice (14). Opioid use in developing countries is still considered inadequate or very inadequate. Indonesia has a relatively low annual average use of only 0.054 mg/capita (15). The use of opioids can cause various complications that can affect the quality of life to varying degrees. In a study at Dr. Soetomo Hospital, 42% of cancer pain patients who received morphine experienced side

effects (16). Morphine is the prototype of opioid analgesics, and oral morphine has been used as the drug of choice in treating moderate to severe cancer pain for over 25 years. Morphine remains the first choice for moderate to severe pain due to better knowledge, availability, and cost compared to other drugs (17).

Cervical cancer is the fourth most frequent cancer in women globally, behind breast cancer, colorectal cancer and lung cancer. In 2018, there were an estimated 570.000 cases of cervical cancer with 311.000 deaths. The estimated age-related incidence of cervical cancer is approximately 13.1 per 100.000 women globally and varies widely among countries (18). In Indonesia specifically, data shows a cervical cancer incidence of 24,4 per 100.000 and a mortality rate of 14,4 per 100.000 (1). The known role of HPV (human papillomavirus) in cervical cancer guides recommendations for early screening in women, facilitating the early discovery of patients with a high potential for cervical cancer. The prognosis of the disease varies based on the stage of the disease. In stage I, the 5-year survival rates are more than 90%, whereas in stage IV, the rate drops to below 20% (19).

Pain is a combination of interactions between sensory, behavioral and emotional aspects as well as personal experiences of pain in the past that can affect a person's response. Pain is also a sensation that arises as an attempt by the body to protect against further damage. According to The International Association for the Study of Pain (IASP), pain is an unpleasant emotional and sensory experience associated with tissue damage that occurs or potentially arises tissue damage (20).

In routine clinical practice, pain is classified into two categories based on duration: acute pain and chronic pain. Chronic pain can be caused by nociception, but psychological and behavioral factors often play a significant role. Acute pain is typically caused by nociception resulting from disease-induced damage or abnormal function of an internal organ tissue or muscle. Pain can also elicit an endocrine stress response leading to metabolic disturbance. Most acute pain can resolve on its own or be managed with therapeutic intervention, but if it persists for more than a month, it becomes chronic pain. Chronic pain is pain that occurs continuously for more than one month, and it can be due to nociceptive, neuropathic, or a combination of both (21).

Patients with cancer have a wide range of complaints that impair their physical and psychological functioning, which can worsen their quality of life. If not properly controlled, pain can have a devastating effect on patients and their families. The importance of pain management as part of routine cancer care has been widely emphasized by the WHO, international and national professional organizations, and government agencies. The prevalence of chronic pain ranges from 30-50% in patients with cancer undergoing active therapy for solid tumors and about 70-90% in advanced

disease. Prospective surveys indicate that about 90% of patients can achieve adequate pain relief with simple drug therapy, but this success is not found in routine practice (9).

Pain in patients with cancer is heterogeneous, and effective management starts with assessment. Assessment should characterize symptoms, clarify the cause of pain, and identify the syndrome. Identification of pain syndromes leads to diagnostic evaluation of specific causes, clarifying the prognosis of the pain or the disease itself. Appropriate and efficient evaluation and therapy require a good understanding of the pain syndrome (22).

Clinically, the main goal of cancer pain classification systems is to improve the quality of pain management. The classification system can identify pain or patient characteristics that indicate difficulty in achieving pain control with the main goal being the patient's quality of life perspective. It also aids the most appropriate choice of therapeutic intervention, the classification system is useful as an effective triage for patients who need a level of care with complexity that suits their needs (14).

Quality of life is a multidimensional concept that refers to an individual's perception of their position in the context of the value system and culture in which they live. It relates to their goals, expectations, and standards and affects a person's physical and psychological state. It can be assumed that the assessment of quality of life must consider aspects of physical health, psychological conditions, autonomous abilities, social relationships, trust, and relationships with the environment (23).

Quality of life can be measured using various instruments and questionnaire modes. However, a questionnaire alone is not enough to describe the entire population, even if it has the same characteristics or needs. In a systematic review, most methodologies were found to be sufficient to describe quality of life, with the most commonly used generic instrument being the EORTC QLQ-C30 (23). The EORTC QLQ-C30 questionnaire consists of 30 questions that cover three areas: global health status, function scale, and symptom scale. The parameters will be calculated based on several questions, and a scale of 0-100 will be obtained. This scale will measure whether a person's quality of life is good or poor in that particular function (24).

Further understanding of the relationship between quality of life and opioid therapy in cancer patients is necessary. This study aims to examine the relationship between quality of life, as assessed by the EORTC QLQ-C30 questionnaire, and daily morphine dose in cervical cancer patients with chronic pain. From the background above, we raised a research question namely: is there a relationship between quality of life and the number of daily morphine doses in cervical cancer patients with chronic pain?

2. Research Method

This study was conducted at the Palliative Clinic of

Dr. Soetomo Hospital from February to March 2023. This type of research was an unpaired categorical comparative analytic observational study with a cross sectional design.

Population and Sample

The population in this study involve patients with cervical cancer in the Palliative Clinic of Dr. Soetomo Hospital who received opioid therapy. Sample in this study includes patients with cervical cancer in the palliative clinic of Dr. Soetomo Hospital who are willing and meet the requirements to become research subjects.

The following are the inclusion and exclusion criteria for a study on patients with cervical malignancy receiving morphine opioid therapy. Inclusion criteria include patients between the ages of 18 to 65 years old with a history of cervical malignancy and are currently receiving morphine opioid therapy. Additionally, patients must be able to communicate effectively, have no hearing or speech impairments, not have any mental retardation or senility, and must be willing to sign an informed consent form. Patients must also have a Karnofsky score of greater than or equal to 50. Exclusion criteria include patients with incomplete medical record data, severe liver or renal disease, lost to follow-up or withdrew from the study, moderate-high levels of anxiety based on HARS, moderately high levels of depression based on HDRS, receiving NSAID therapy other than paracetamol, received acupuncture therapy, psychotherapy, or any other non-pharmacological therapy in the past week, and patients who have been hospitalized in the past week.

The consecutive random sampling technique involves including all subjects who meet the selection criteria until the desired number of subjects is reached. The minimum sample size was calculated using the correlation sample formula (25), and accounting for an estimated dropout rate of 10%, the minimum sample size for this study was determined to be 41 patients. Research Instruments includes Medical record and EORTC QLQ-C30 questionnaire in Indonesian language.

Research Procedure

This study involved a general set of steps to ensure

the participation and consent of patients and their families. First, the researcher provided an explanation of the study and a written information sheet to each patient or family, and they were given the opportunity to ask any questions they had. After understanding the nature of the study, the patients or families provided consent by signing an informed consent form. The explanation of the study was delivered in simple language that was easily understandable by the patients and their families. Next, the patients completed the provided questionnaire, which assessed their quality of life and other relevant factors related to their condition. Participation in the study was free of charge for the patients and their families. This ensured that the patients did not incur any additional financial burden while participating in the study. Overall, the research procedures were designed to prioritize the comfort and understanding of the patients and their families.

Data Collection

The data collected from the study will be processed and analyzed using various methods. The collected data will be recorded and tabulated, and processed using the Statistical Package for Social Sciences (SPSS) application. Descriptive statistics will be used to summarize the data, including mean and standard deviation for quantitative (numeric) values, and number and percentage for categorical values.

Statistics

To determine the relationship between the quality of life and daily opioid dose of cervical cancer patients with chronic pain, the Pearson test will be used for normally distributed data, while Spearman's rank correlation will be used for data with abnormal distributions. The statistical significance of the results will be determined using a p-value of less than 0.05, which indicates a strong likelihood that the results are not due to chance. Overall, the data processing and analysis methods will be used to evaluate the relationship between quality of life and daily opioid dose and provide insights into the efficacy of opioid therapy in managing chronic pain in cervical cancer patients.

Research Design

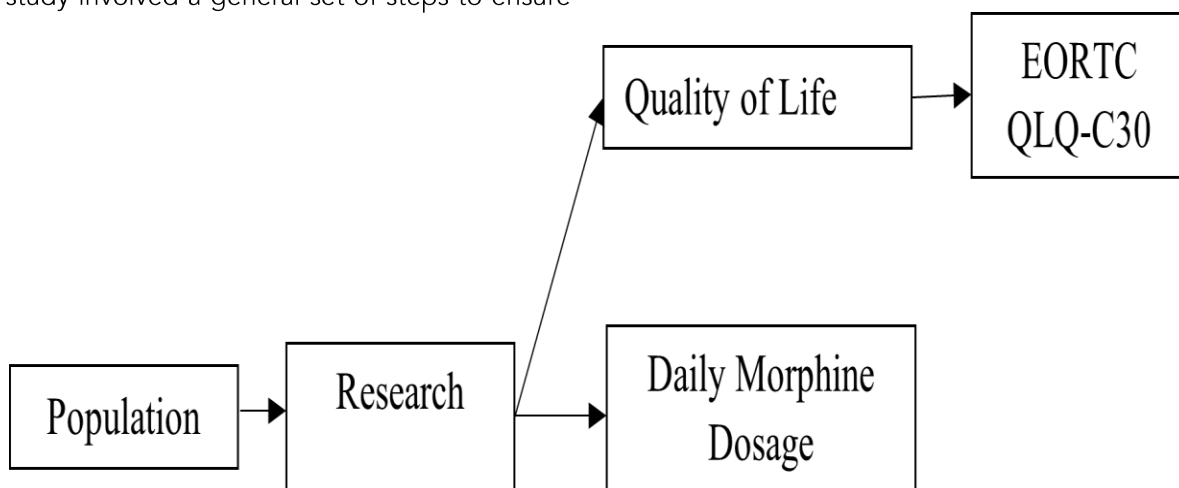


Figure 1: Research design

Conceptual Framework

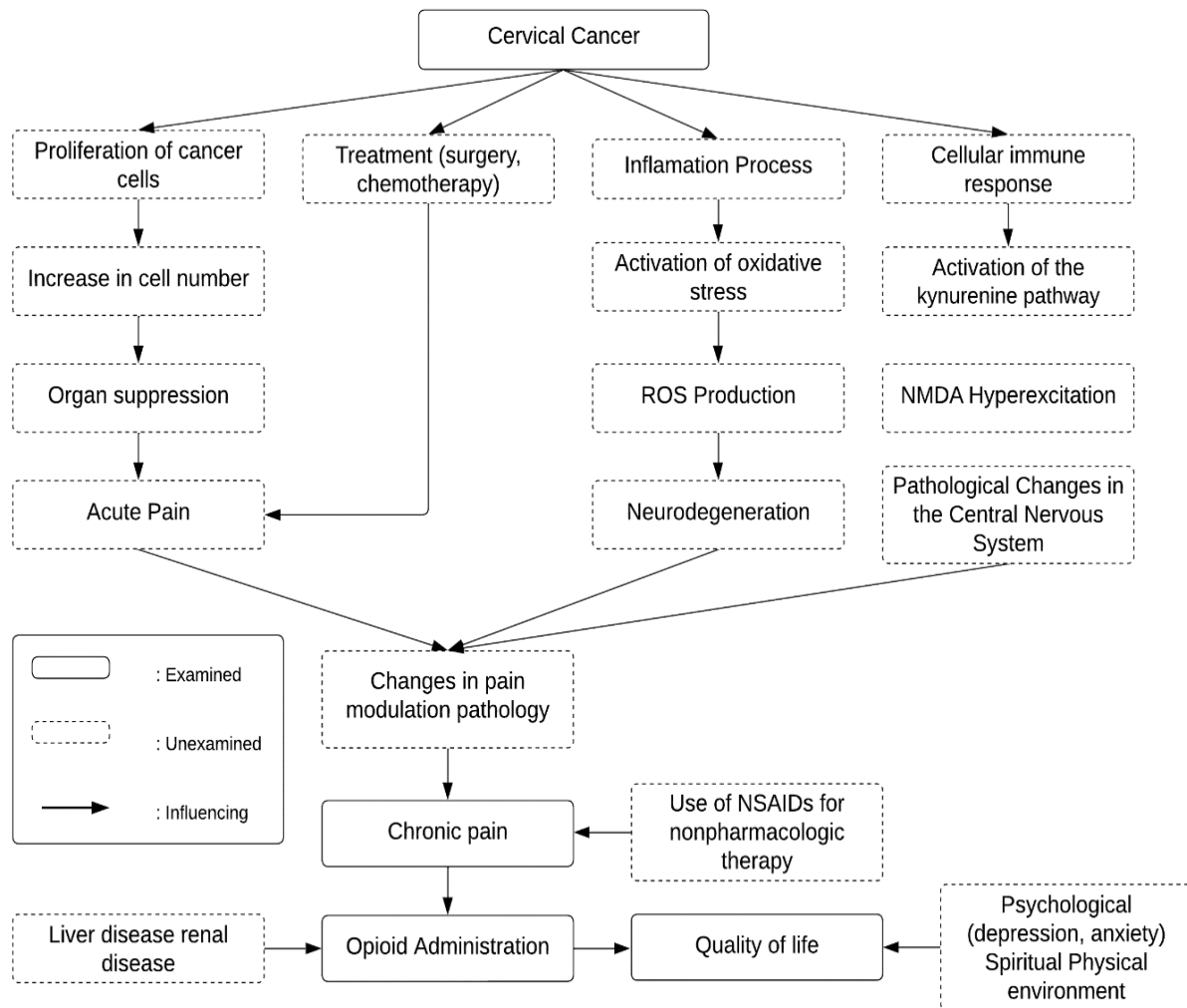


Figure 2: Conceptual Framework

The process of malignancy gives rise to complex mechanisms that enhance the body's response, and uncontrolled cell proliferation can cause mechanical stress on surrounding organs, leading to visceral pain. If left untreated, this pain can progress into chronic pain. Additionally, patients who receive both operative and medical therapy may also experience pain. Poorly managed acute pain can cause changes in pain modulation, ultimately leading to increased opioid dosages as a pain management strategy in cases of malignancy.

In malignancies, a chronic inflammatory process occurs, leading to the activation of oxidative stress that produces reactive oxygen species (ROS). These ROS can cause damage to DNA and mitochondria in cells and play a role in the pathology of pain modulation changes through post-transcriptional modifications that cause neurodegeneration processes, long-term abnormal hippocampal potentiation, impaired synaptogenesis, and neuronal survival. The cellular immune response also shifts the tryptophan pathway to the kynurenine pathway, resulting in decreased serotonin and increased activation of the kynurenine pathway. The derivative of the kynurenine pathway is neuroactive, as it

occupies NMDA receptors. An imbalance of kynurenine derivatives will result in hyperexcitation of NMDA receptors, causing pathological changes in central nervous system neurons that trigger chronic pain symptoms.

Patients with chronic pain that is moderately severe or worse may require opioids for management. The optimal dose of opioids should be adjusted based on the patient's symptoms and any coexisting medical conditions. In addition, the use of NSAIDs and non-pharmacological therapies, such as acupuncture, can also have an impact on the pain experienced by cancer patients with chronic pain.

The administration of opioids can affect a patient's pain level and therefore their quality of life. However, there are several other factors that can also affect quality of life, such as spirituality, psychological well-being, non-pharmacological therapies, environment, and physical function.

3. Results and Discussion

Characteristics of Research Subjects

This study involved 42 patients who visited the palliative clinic from February to March 2023 and met

the inclusion and exclusion criteria. The research subjects were patients with cervical cancer, with 30 patients (71.4%) in stage 3 and 12 patients (28.6%) in

stage 4. Based on age, the median age of the patients in this study was 50 years (ranging from 27 to 63 years) with a mean of 48.79 years.

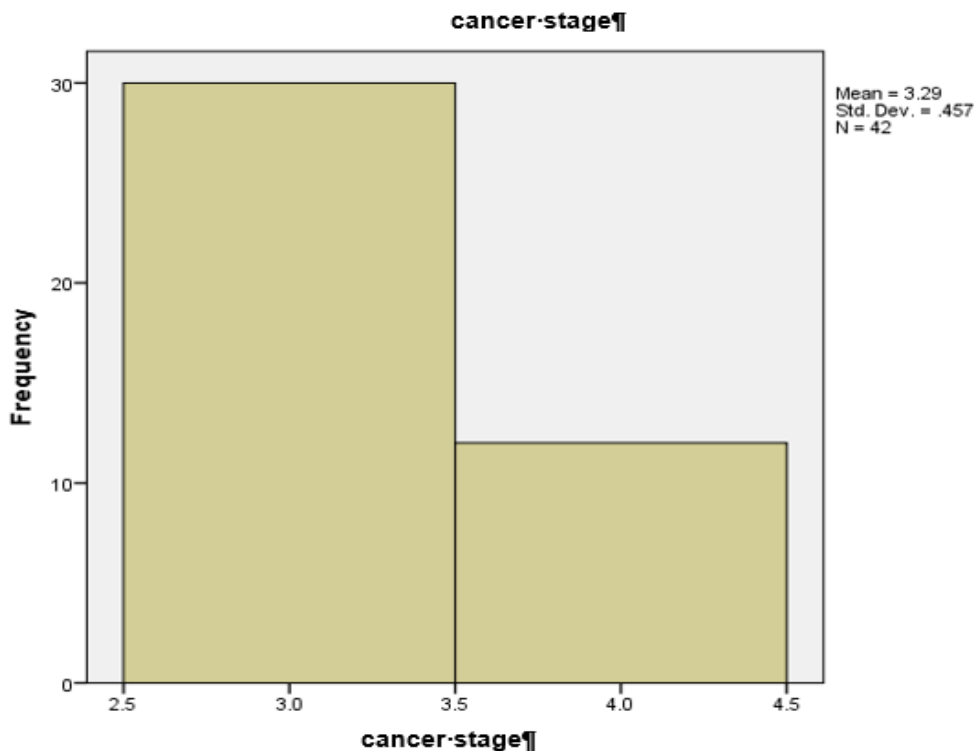


Figure 3: Cancer stage frequency

In this study, the degree of pain was measured using the NRS pain scale when the patients visited the Palliative Clinic of Dr. Soetomo Hospital. The NRS pain scale uses a numerical scale from 0 to 10. The most frequent pain scale reported was 2, with 10 patients (33.3%) experiencing that level of pain. The lowest pain scale reported by a subject was 1, and the highest was 5.

Regarding the daily use of morphine, the average was 50.24 mg/day, ranging from a minimum of 20

mg/day to a maximum of 120 mg/day. The administration interval of morphine ranged from 2 to 6 times per day, with the majority of subjects receiving morphine doses 4 times a day, as reported by 28 patients (66.7%).

From the normality test of the data on the characteristics of the study subjects, it was found that all patient characteristics in this study were not normally distributed ($p < 0.05$). The characteristics of this study are summarized in table 1.

Table 1: Characteristics of Research Subjects

Variable	Mean + SD	Median (Min-max value)	N (%)	p* value
Age (years)	48.79 ±8.94	50 (27-63)		0,065
Cancer Staging				
3			30 (71,4)	<0.001
4			12 (28,6)	
NRS Pain Scale				0,001
1			3 (7,1)	
2			17 (40,5)	
3			10 (23,8)	
4			9 (21,4)	
5			3 (7,1)	
Daily Morphine Dosage (mg/day)	50.24 ±23.79	50 (20-120)		0,003
Interval				<0.001
2x/day			1 (2,4)	
4x/day			28 (66,7)	
6x/day			13 (31,0)	

*normality test with Saphiro-Wilk test

Quality of Life of Study Subjects

In this study, quality of life was examined using the EORTC QLQ C-30 questionnaire which assessed various parameters. The parameters assessed

included global health status, physical function, role function, emotional function, cognitive function, social function, fatigue, nausea and vomiting, pain, shortness of breath, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties. Each

parameter has a value of 0 to 100. From the validity test of the questionnaire using the Pearson correlation product moment test, it was

found that all question items were valid. Table 2 shows the validity test results of the EORTC QLQC-30 questionnaire

Table 2: Validity test results

Question Number	R value	p value
1	0,486	0,001
2	0,607	<0,001
3	0,774	<0,001
4	0,862	<0,001
5	0,613	<0,001
6	0,518	0,001
7	0,527	0,001
8	0,685	<0,001
9	0,813	<0,001
10	0,711	<0,001
11	0,641	<0,001
12	0,733	<0,001
13	0,464	0,002
14	0,622	<0,001
15	0,595	<0,001
16	0,418	0,006
17	0,665	0,026
18	0,602	<0,001
19	0,640	0,001
20	0,539	<0,001
21	0,545	0,001
22	0,732	<0,001
23	0,643	<0,001
24	0,568	0,001
25	0,412	0,007
26	0,611	<0,001
27	0,598	0,008
28	0,369	0,016
29	0,903	<0,001
30	0,855	<0,001

*questions are considered valid if $p < 0.05$ and $r > 0.361$ ($n=30$)

Based on the global health status represented by questions 29 and 30, the mean score was 64.09 ± 11.71 , with the lowest value of 50 and the highest value of 91.67. In the reliability test, Cronbach's Alpha of 0.755 was obtained.

On the physical function scale represented by questions 1 to 5, the mean value is 72.54 ± 14.96 with the lowest value of 0 and the highest value of 93.3. The internal consistency value of this scale, as measured by Cronbach's Alpha, is 0.849. On the role function scale represented by questions 6 and 7, the average value is 76.98 ± 16.44 with the lowest value of 33.3 and the highest value of 100. The reliability test using Cronbach's alpha yielded a value of 0.802. On the emotional function scale represented by questions 21 to 24, the average value is 75.59 ± 13.32 with the lowest value of 50 and the highest value of 100. The Cronbach's alpha reliability test yielded a value of 0.866. On the cognitive function scale represented by questions 20 and 25, the average value is 90.48 ± 14.32 with the lowest value of 66.7 and the highest value of 100. The Cronbach's alpha reliability test yielded a value of 0.871. On the social function scale represented by questions 26 and 27, the average value is 90.48 ± 18.09 with the lowest value of 66.7 and the highest value of 100. The reliability test using Cronbach's alpha yielded a

high value of 0.961.

On the fatigue scale represented by questions 10, 12, and 18, the average value is 25.39 ± 17.40 with the lowest value of 0 and the highest value of 55. From the reliability test with Cronbach's alpha, a value of 0.862 was obtained. On the nausea and vomiting scale represented by questions 14 and 15, the mean value is 12.69 ± 15.96 with the lowest value of 0 and the highest value of 33.3. From the reliability test with Cronbach's alpha, a value of 0.949 was obtained. On the pain scale represented by questions 9 and 19, the mean value was 27.38 ± 21.09 with the lowest value of 0 and the highest value of 66.7. From the reliability test with Cronbach's alpha, a value of 0.789 was obtained. On the shortness of breath scale represented by question 8, the mean value is 7.14 ± 13.84 with the lowest value of 0 and the highest value of 33.3. On the sleeplessness scale represented by question 11, the average value is 16.67 ± 16.87 with the lowest value of 0 and the highest value of 33.3. On the scale of decreased appetite represented by question 13, the average value is 12.69 ± 17.96 with the lowest value of 0 and the highest value of 66.7. On the constipation scale represented by question 16, the average value is 30.95 ± 21.32 with the lowest value of 0 and the highest value of 66.7. On the diarrhea

scale represented by question 17, the average value is 8.73 ± 14.83 with the lowest value of 0 and the highest value of 66.7. On the scale of financial difficulties represented by question 28, the average value is 0.79 ± 5.14 with the lowest value of 0 and the highest value of 33.3. The six scales were not

tested for internal consistency because each scale was only represented by one question. A summary of the results of the calculation of quality of life based on the EORTC QLQC-30 questionnaire can be seen in Table 3.

Table 3: List of mean, minimum, maximum and Cronbach's alpha coefficient of EORTC QLQC-30 questionnaire

Scale	Mean + SD	Min – Max	Cronbach's Alpha
Global health status	64.09 ±11.71	50 – 91,7	0,755
Physical functions	72.54 ±14.95	0 – 93,3	0,849
Role functions	76.98 ±16.44	33,3 - 100	0,802
Emotional functioning	75.59 ±13.32	50 - 100	0,866
Cognitive function	90.48 ±14.32	66,7 - 100	0,871
Social functions	90.48 ±18.09	33,3 - 100	0,961
Fatigue	25.39 ±17.40	0 – 55,5	0,862
Nausea, vomiting	12.69 ±15.96	0 – 33,3	0,949
Pain	27.38 ±21.09	0 – 66,7	0,789
Shortness of breath	7.14 ±13.84	0 – 33,3	-*
Difficulty sleeping	16.67 ±16.87	0 – 33,3	-*
Lost appetite	12.69 ±17.96	0 – 66,7	-*
Constipation	30.95 ±21.32	0 – 66,7	-*
Diarrhea	8.73 ±14.83	0 – 33,3	-*
Financial difficulties	0.79 ±5.14	0 – 33,3	-*

* Not counted because only 1 question item

Relationship between Subject Characteristics and Daily Morphine Dose

In this study, there was no difference in daily morphine dose in the patient's cancer stage. From the results of the Mann-Whitney t-test, the difference

in daily morphine levels at the cancer stage obtained a significance value of $p=0.576$. Where in stage 3, the average morphine dose used was 48.33 ± 20.35 mg/day and in stage 4, the average daily morphine dose used was 55 ± 28.44 mg/day.

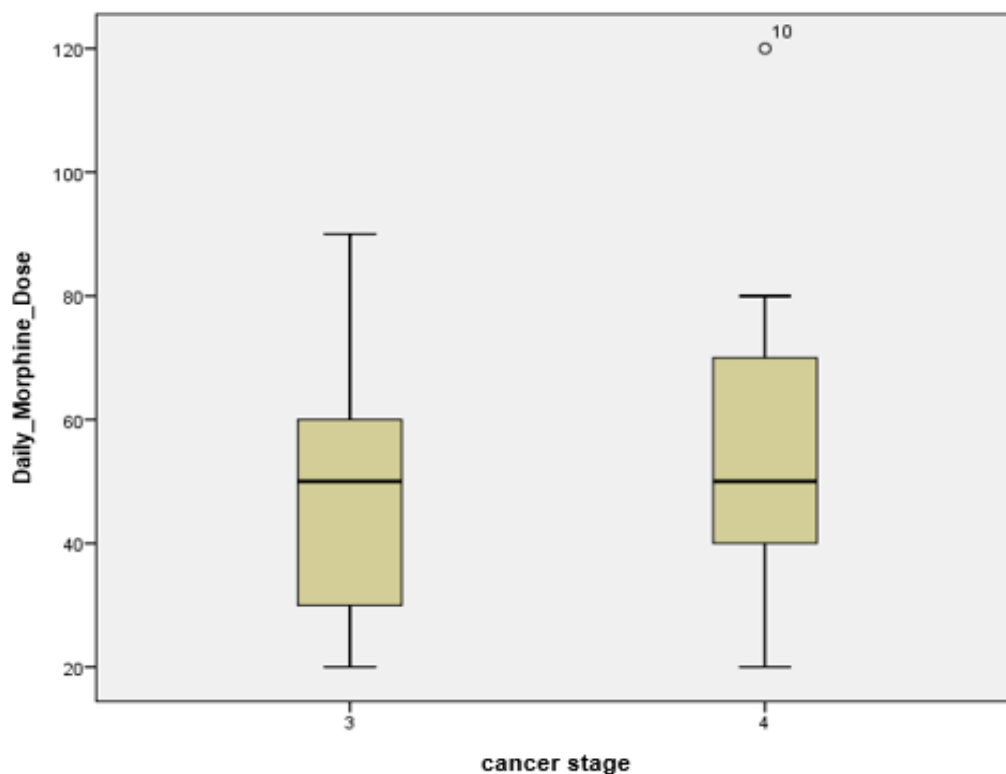


Figure 4: Morphine dose distribution by cancer stage

Based on the degree of pain, there was a significant relationship between the degree of pain and the number of daily morphine doses with a significance of $p=0.040$. This relationship was a moderate positive correlation with $r=0.318$. The subject with

the highest NRS score in this study, which was 5, received the highest average dose of 86.67 mg/day. The number of daily morphine doses based on the degree of pain can be seen in Table 4.

Table 4: Daily morphine dose based on degree of pain

NRS pain scale	Mean Daily Morphine Dose ±SD (mg/day)	p value	R value
1	46,67 ±11,64	0,040	0,318
2	43,53 ±19,98		
3	47,00 ±20,02		
4	55,56 ±22,42		
5	86,67 ±30,55		

Correlation of Quality of Life with Daily Morphine Dose

The Spearman correlation test showed a significant relationship between daily morphine dose and quality of life in the global quality of life scale ($r=-0.467$, $p=0.002$), pain symptom scale ($r=0.363$, $p=0.018$), and constipation symptom scale ($r=0.418$, $p=0.006$). However, there was no significant correlation with daily morphine dose for the other scales ($p>0.05$). Based on the correlation test results, a correlation coefficient of $r=-0.467$ was obtained for the global quality of life scale of the EORTC QLQ C-30 questionnaire and daily morphine dose. This means that there is a moderate negative correlation between quality of life on the global quality of life scale and daily morphine dose. Therefore, it can be concluded that the higher the morphine dose, the

lower the global quality of life scale on the EORTC QLQC-30 questionnaire.

Regarding the pain symptom scale and constipation symptom scale, the correlation coefficients were 0.363 and 0.418, respectively. This indicates a moderate positive correlation between daily morphine dose and quality of life on these scales. In other words, higher morphine doses were associated with higher scores on the pain and constipation symptom scales of the EORTC QLQC-30 questionnaire. However, there was no significant correlation between daily morphine dose and the other scales ($p>0.05$). Moreover, this study found no significant correlation between the interval of drug administration and the quality of life of cervical cancer patients with chronic pain ($p>0.05$).

Table 5: Correlation of quality of life with daily morphine dose

Variable	R value	P value
Global health status	-0,467	0,002
Physical functions	-0,137	0,388
Role functions	0,013	0,936
Emotional functioning	-0,044	0,781
Cognitive function	-0,212	0,178
Social functions	-0,030	0,850
Fatigue	0,079	0,618
Nausea, vomiting	0,021	0,896
Pain	0,363	0,018
Shortness of breath	0,111	0,484
Difficulty sleeping	-0,022	0,889
Lost appetite	0,019	0,906
Constipation	0,418	0,006
Diarrhea	0,150	0,345
Financial difficulties	-0,232	0,139

Table 6: Correlation of quality of life with drug administration interval

Variable	R value	P value
Global health status	0,023	0,884
Physical functions	-0,005	0,973
Role functions	-0,044	0,781
Emotional functioning	0,176	0,264
Cognitive function	0,005	0,974
Social functions	0,111	0,485
Fatigue	-0,059	0,711
Nausea, vomiting	-0,122	0,441
Pain	0,136	0,391
Shortness of breath	-0,076	0,633
Difficulty sleeping	0,112	0,478
Lost appetite	0,050	0,754
Constipation	0,121	0,444
Diarrhea	-0,215	0,172
Financial difficulties	-0,094	0,553

4. Discussion

Characteristics of Research Subjects

This study included 42 cervical cancer patients with

chronic pain, with stage 3 and 4. The mean age of the study participants was 48 years, and the average daily morphine use was 50.24 mg/day.

In a study conducted in Mexico, the average morphine use was 20 (12-30) mg/day (26), but this

study included all types of cancer. Another study showed an average daily morphine dose of 56.66 mg/day (27), but the subjects in that study had severe cancer pain regardless of chronicity.

In terms of quality of life, this study obtained data on the mean value of global health status 64.09. On the function scale, the lowest mean was obtained on the physical function scale and the highest mean on the social function scale. For the mean value of the symptom scale, the lowest value on the financial difficulty scale and the highest value on the pain scale.

In another study, the mean score for the global health status scale was 58.7 (7). The lowest and highest values on the function scale were different, where the lowest score was found for the role function scale and the highest score was found for the cognitive function scale. On the symptom scale, the lowest score was obtained for the diarrhea scale and the highest score was obtained for the financial difficulty scale. The differences between this study and Perwitasari et al. (7) can be attributed to several factors, including the types of cancer included in the study and the criteria for opioid therapy determination. Perwitasari et al. (7) included various types of cancer, although cervical cancer was the dominant cancer (60.1%). Patients who had received opioid therapy within the last 2 weeks were excluded from the study.

This study illustrates a better global health scale compared to previous studies conducted in Indonesia. Differences in cultural factors can be one of the causes of differences in global health scale values (23). Although both studies were conducted in two tertiary healthcare centers in major cities on the island of Java, there are differences in terms of culture.

Relationship between Quality of Life and Daily Morphine Dose

Current study found a correlation between quality of life and daily morphine dose. Spearman correlation test showed a significant correlation on the global health status scale with daily morphine dose. This significant relationship was moderate in strength. This negative correlation coefficient can be interpreted as the lower the pain symptom scale, the higher the daily morphine dose.

As for the pain and constipation symptom scales, there was a significant relationship with daily morphine dose, respectively. This indicates a positive relationship between pain and constipation symptom scale and daily morphine dose. This result can be interpreted that if the pain and constipation symptom scale increases, the daily morphine dose will also increase. For other scales, there was no significant relationship with daily morphine dose. Likewise, there was no significant relationship between the interval of drug administration and the quality of life scale with the EORTC QLQ-C30.

The use of morphine for chronic pain management in cancer patients is known to have several benefits. After codeine therapy, the use of morphine, whether

immediate or slow release, is known to significantly reduce the pain scale on the quality of life with the EORTC QLQ C-30 questionnaire. Moreover, the use of morphine does not affect the function scale on the EORTC, including physical, role, emotional, cognitive, and social function (28).

Several studies have investigated the relationship between quality of life and daily opioid dose. These studies found a significant correlation between quality of life and daily opioid dose. For instance, Karafin et al. (29) conducted a study on sickle cell disease patients with chronic pain and found that patients with opioid doses >90 MME per day had a worse quality of life. The study also found that higher doses of opioids were related to chronic pain. Similarly, a study in Iceland found a weak positive correlation between quality of life on several symptom scales and opioid doses (30). Managing chronic pain using opioids can improve quality of life, adherence to cancer treatment, reduce emotional stress, and also have a positive effect on survival rates (31).

The significant results obtained on the global health scale, pain symptom scale, and constipation symptom scale in this study highlight the importance of regulating and strictly evaluating the use of morphine doses. While the global health status of the subjects tended to be better compared to previous studies, further research with a broader research design and larger sample size is required to obtain a more accurate representation of the population.

Furthermore, the results of this study suggest that the EORTC QLQ-C30 questionnaire can provide a comprehensive picture of quality of life and its relationship with morphine, making it a valuable tool for clinicians in evaluating the use of morphine and patient conditions. This evaluation is particularly important in pain management to ensure that patients receive comprehensive therapy. The questionnaire can also serve as a measuring point for healthcare providers to determine therapeutic targets for patients. However, other parameters such as pain scale and psychological examination are necessary to support the patient's therapy plan.

High scores on the pain and constipation symptom scales with high doses of morphine should be of concern to clinicians. Currently, the development of oral opioids has advanced, and there are other options besides morphine that can be given to outpatients. Opioids that are more potent than morphine, such as oxycodone, can be considered for patients who are already receiving high doses of morphine. Transdermal opioid therapy is also known to help improve patients' quality of life (32). According to the CDC (2016), opioid doses >50 MME increase overdose rates compared to those receiving <20 MME.

In addition, the multimodal therapy offered by the WHO can be the subject of multidisciplinary discussion to achieve a better quality of life for patients. Invasive measures can be considered for

cervical cancer patients with chronic pain to help manage persistent pain after high-dose opioids. Continuous epidural administration of drugs and impar ganglion block can be an alternative offered if pain or quality of life does not improve after high-dose morphine administration. Indeed, this treatment should be adjusted to the location of pain that is most felt by the patient.

This study has several limitations that need to be considered. First, the research design used was cross-sectional, which means that there is a possibility of bias from other factors that affect the outcome of the study's results. Although the criteria for research subjects have tried to be as homogeneous as possible, the cross-sectional design may limit the study's ability to draw definitive conclusions about the relationship between quality of life and daily morphine dose. Second, data on morphine use was not comprehensive until the duration of morphine use, which may have affected the accuracy of the results. Third, the data used in this study was obtained from only one healthcare center, which limits the generalizability of the findings to other populations. These limitations indicate the need for further research with more comprehensive data and a broader research design to obtain a more accurate picture of the relationship between quality of life and daily morphine dose in cancer patients.

5. Conclusion

Based on the statistical analysis and discussion in this study, the following conclusions can be drawn:

1. This study found that the EORTC QLQ C-30 questionnaire was valid and reliable for use in cervical cancer patients with chronic pain.
2. The data on daily morphine use obtained in this study showed an average of 50.24 mg/day, with the lowest value of 20 mg/day and the highest value of 120 mg/day.
3. There was a significant relationship between the global health scale, pain symptom scale, and constipation symptom scale on the EORTC QLQ C-30 questionnaire with daily morphine dose. Specifically, a higher global health scale was associated with a lower daily morphine dose. The strength of the relationship (r) between the global health status scale and daily morphine dose was -0.467 , indicating a moderate relationship. Conversely, a higher pain symptom scale and constipation symptom scale were associated with a higher daily morphine dose. The strength of the relationship (r) between the pain and constipation symptom scale and daily morphine dose was 0.363 and 0.418 , respectively, indicating a moderate relationship between the scales and morphine dose.

Prospective studies are needed to assess the clinical significance of morphine doses on the quality of life of cervical cancer patients with chronic pain. Further research is needed to compare the duration of

morphine use in order to assess the impact on the quality of life of cervical cancer patients with chronic pain.

Conflict of Interest

The authors hereby declare that there is no conflict of interest in this study.

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Author Contribution

- A. Fikri Bariz -contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.
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