THE RELATIONSHIP BETWEEN LONGTERM USE OF MORPHINE AND COGNITIVE FUNCTION IN CERVICAL CANCER PATIENTS AT THE PALLIATIVE CARE CLINIC OF DR. SOETOMO HOSPITAL IN SURABAYA

Aji Mustika Ningrum[1], Christrijogo Sumartono[2], Wiwiek Indriyani Maskoep[2], Yunias Setiawati[2], Maulydia[2], Belindo Wirabuana[2], Atika[2]

1Specialist-1 Medical Education Program, Anesthesiology and Intensive Therapy Study Program, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Regional General Hospital, Surabaya, Indonesia. (Corresponding Author)

2Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Regional General Hospital, Surabaya, Indonesia.

Objectives: Cervical cancer is one of the most common gynecological cancers found in women worldwide. Cervical cancer ranks 14th among all cancers and 4th among cancers in women. Pain is the most common symptom experienced by patients with advanced cervical cancer. Most women with cervical cancer are likely to experience moderate to severe pain. Morphine is one of the strong opioids that are often given in the management of moderate to severe cancer pain. However, morphine has been associated with negative effects on cognitive function such as memory impairment, delayed reaction time, and memory loss. This study aims to analyze the pain level of cervical cancer patients, analyze the relationship between longterm use of morphine and cognitive function, and analyze the relationship between morphine dose and cognitive function.

Methodology: A cross-sectional study with 47 subjects consisting of women with cervical cancer. Pain scale measurement using Numeric Rating Scale with a scale of 0-10, Subjects were interviewed and guided to fill out the Mini Mental State Examination questionnaire for cognitive function with a scale of 0-30. And daily morphine use was seen from medical records.

Results: This study showed that the majority of cervical cancer patients with mild pain were 26 people (55.3%). From the Chi Square correlation test results, there was no relationship between the longterm use of morphine and cognitive function, as evidenced by the value of $p > 0.05$, which is 0.572. And from the Spearman test there was no relationship between morphine dose and cognitive function, as evidenced by the value of $p > 0.05$, which is 0.094 with $r = 0.247$. Although statistically there was no relationship, subjects who used morphine for more than 12 months had lower scores for orientation, attention, calculation, recall, and language compared to subjects who used morphine for 6 to 12 months.

Conclusion: Longterm use of morphine is not related to cognitive function.

Keywords: Cervical Cancer, Longterm use of Morphine, Cognitive Function, MMSE, Psychological Well-Being.

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INTRODUCTION

Cervical cancer is a significant global health concern, ranking 14th among all cancers and 4th among cancers in women, with approximately 500,000 new cases and 250,000 deaths annually (Josephine R Fowler et al., 2022). Pain is a common and distressing symptom, especially in advanced cervical cancer patients, impacting both physical and psychological well-being (Gress et al., 2020; Makhlouf et al., 2020). Effective pain management is crucial and involves various therapies, including opioids (World Health Organization, 2018). Morphine, a potent opioid, is often used for moderate to severe cancer pain and can provide significant relief (Schug et al., 1992b; Philip J Wiffen et al., 2016).

However, the use of morphine has been associated with adverse effects on cognitive function, including memory impairment and reduced attention (Osowicka, 2019). Despite its efficacy in pain relief, understanding the potential impact of longterm morphine use on cognitive function is essential, especially in cervical cancer patients. The study aims to explore this correlation, contributing to a better understanding of cognitive function in the context of cancer care (Cherrier et al., 2009; Hindmarch et al., 2005; Salinsky et al., 2010; Sjøgren et al., 2000).

Additionally, cervical cancer's early diagnosis and prevention through factors like sexual history, HPV testing, and vaccination are vital (National Cancer Institute, 2011; Burmeister et al., 2022). Pain assessment,

particularly pain intensity measurement, plays a critical role in tailoring effective pain management strategies (Caraceni & Shkodra, 2019). Furthermore, cancer's impact on cognitive function, including attention, memory, and information processing speed, is another crucial aspect of care (Abebe et al., 2021; Sudo & Ando, 2020). This study seeks to shed light on these interconnected aspects of care to provide more comprehensive support to cervical cancer patients, particularly those receiving longterm morphine therapy at the Palliative Care Clinic of Dr. Soetomo Surabaya Hospital.

METHODOLOGY

This research utilized a correlational analytic observational approach with a cross-sectional design. Primary data were collected through direct interviews to obtain MMSE scores, while secondary data included various characteristics, pain scale assessments, morphine dosage, longterm use of morphine, and treatment history. The study took place at the Palliative Care Clinic of Dr. Soetomo Hospital in Surabaya and commenced after obtaining ethical clearance from the Health Research Ethics Committee of Dr. Soetomo Surabaya Hospital. It continued until the minimum required sample size was achieved. The research focused on adult patients diagnosed with cervical cancer who underwent longterm morphine therapy at the Palliative Care Clinic of Dr. Soetomo Surabaya Hospital during July to August 2023. The sample size was calculated using the correlation formula, resulting in a minimum sample size of 47. Sampling was performed using the consecutive sampling method, involving all eligible subjects willing to participate in the study.

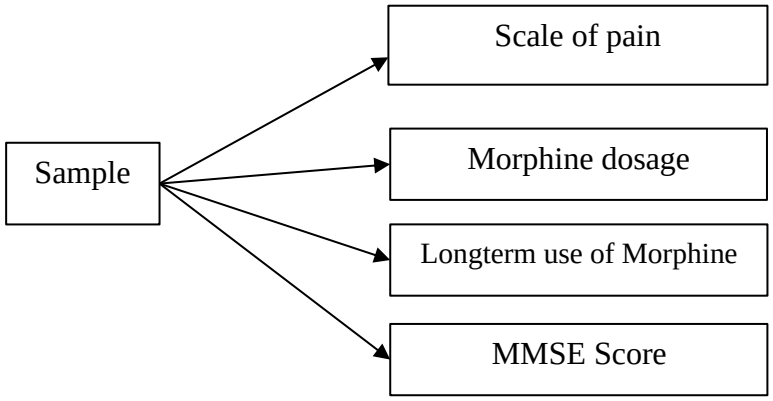

Figure (1) Research design

For inclusion in this study, we are considering patients who fall within the age range of 18 to 64 years. Specifically, we are focusing on individuals who are chronic pain patients and have received a diagnosis of cervical cancer. Furthermore, our inclusion criteria extend to those who have been undergoing morphine therapy for a minimum of six months and are willing to participate as research subjects. On the other hand, exclusion criteria are in place to ensure the study's integrity. Patients with pre-existing cognitive impairment before commencing morphine therapy are excluded. Additionally, individuals currently receiving steroid therapy, those with metastasis to the central nervous system, and those diagnosed with renal or liver failure are also excluded from the study. History of stroke or cerebrovascular disease is another criterion for exclusion. Patients who voluntarily withdraw from the study or have incomplete medical record data will not be considered for participation.

In this study, the independent variable is the longterm use of morphine, while the dependent variable is cognitive function, assessed through the Mini-Mental State Examination (MMSE) score. The research materials include medical records of cervical cancer patients treated at the Palliative Care Clinic of Dr. Soetomo Hospital in Surabaya who agreed to participate and the MMSE questionnaire translated into Indonesian for cognitive function assessment. The research employed various tools, including an informed consent sheet to ensure participant understanding and voluntary consent, as well as a data collection sheet for systematic data recording. The research method involved structured interviews conducted by trained doctors at the Palliative Care Clinic using the MMSE questionnaire and the collection of comprehensive medical record data, including age, gender, diagnosis, morphine dosage and longterm use of morphine, number of visits, pain scale assessments, and treatment history.

Data collection in this study utilized a customized Data Collection Sheet (DFS). The research results were presented through tabulation, graphs or diagrams, and written explanations to clarify the visual representations. Data analysis was carried out using Microsoft Excel and

SPSS Statistics software, involving several steps. Firstly, univariate analysis was employed to examine the demographic and clinical characteristics of the study subjects, presented as frequency and percentage distribution tables. Secondly, bivariate analysis included the Chi-Square test to assess the relationship between the longterm use of morphine and the cognitive function of cervical cancer patients, and the Spearman test to evaluate the relationship between morphine dosage and cognitive function in these patients. The significance level maintained throughout the analysis was 5%, where a p-value of <0.05 was considered statistically significant.

Operational framework

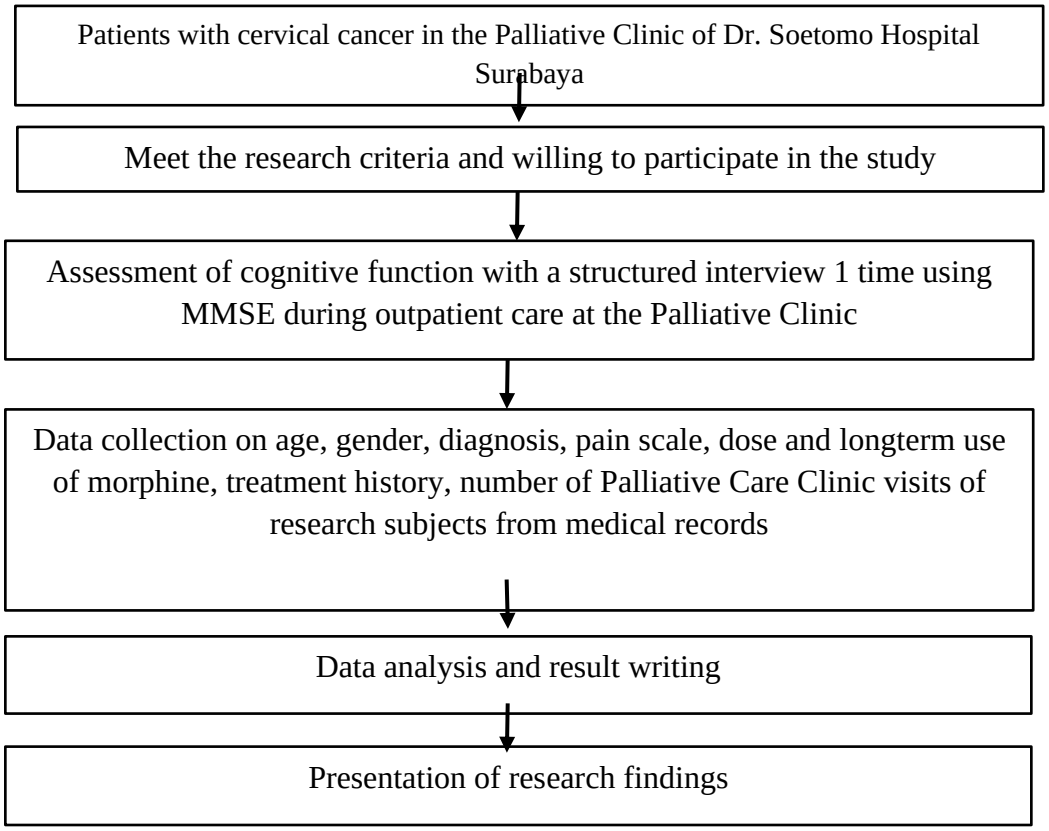

Figure (2) Operational framework of the study

RESULTS

Characteristics of Research Subjects

This study was conducted at the Palliative Care Clinic of Dr. Soetomo Hospital, involving 47 cervical cancer patients who attended the clinic between July and August 2023 and met the specified inclusion and exclusion criteria. **Table 1** provides an overview of the research subjects, revealing that the majority of patients had cervical cancer at stage 3, totaling 28 individuals (59.6%). In terms of age, the median age of the patients in this study was 55 years, ranging from 28 to 64 years, with an average age of 51.96 years.

Additionally, educational data were collected in the study. The findings indicate that 7 individuals (14.9%) had not received any formal education, 15 (31.9%) had completed elementary school, 7 (14.9%) had finished junior high school, 12 (25.5%) had attained a high school or vocational school education, 3 (6.4%) had completed D3 programs, and 3 (6.4%) had achieved S1 qualifications.

Regarding the daily use of morphine, doses ranged from a minimum of 2.5 mg to a maximum of 7.5 mg, with varying administration frequencies throughout the day. According to clinic records, the most common morphine

administration regimen was 4 times daily at 5 mg each, accounting for 22 patients (46.8%), while the lowest frequency was 6 times daily at 2.5 mg each, which was observed in only 1 individual (2.1%).

Table (1) Characteristics of Study Subjects

Variable	Min - Max	Mean	Median	N(%)
Age (years)	28-64	51,96	55	
Stage				
2				16 (34)
3				28 (59,6)
4				3 (6,4)
Education level				
No Formal education				7 (14,9)
Primary school				15 (31,9)
Junior high school				7 (14,9)
Senior/Vocational high school				12 (25,5)
Diploma				3 (6,4)
Bachelor				3 (6,4)
Morphine Dosage				
4 x 2,5 mg/day				17 (36,2)
4 x 5 mg/day				22 (46,8)
4 x 7,5 mg/day				5 (10,6)
6 x 2,5 mg/day				1 (2,1)
6 x 5 mg/day				2 (4,2)

Description of Research Variables

In this study, the degree of pain was assessed using the Numerical Rating Scale. The results indicated that the highest number of patients reported experiencing mild pain, with a total of 26 individuals (55.3%), while the lowest number reported either no pain or severe pain, with both categories comprising 3 people each (6.4%).

Table (2) Pain Scale Characteristics

Degree of Pain	Frequency (%)
No Pain	3 (6,4)
Mild Pain	26 (55,3)
Moderate Pain	15 (31,9)
Severe Pain	3 (6,4)
Total	**47**

The assessment of cognitive function in this study utilized the Mini Mental State Examination (MMSE) questionnaire to evaluate various parameters, including orientation, registration, attention calculation, recall, and language. Each parameter was individually assessed and subsequently summed to produce a value within the range of 0-30. The classification system for MMSE scores categorizes scores of 24-30 as normal, 17-23 as indicative of probable cognitive impairment, and 0-16 as indicative of definite cognitive impairment. The responses obtained from the MMSE questionnaire are presented in **Table 3**, categorized based on the longterm use of morphine, specifically between 6 to 12 months and over 12 months.

Table (3) Subjects' answers to the research questionnaire

Cognitive Function	Morphine 6 - 12 months	Morphine for more than 12 months
	N (%)	N (%)
Orientation Score		
10	23 (69,7)	4 (28,57)
9	6 (18,2)	7 (50)
8	2 (6,1)	2 (14,28)
7	2 (6,1)	1 (7,14)
< 7	0 (0)	0 (0)
Registration score		
3	33 (100)	14 (100)
< 3	0 (0)	0 (0)

Attention & Calculation Score		
5	13 (39,4)	3 (21,42)
4	7 (21,2)	6 (42,85)
3	9 (27,3)	4 (28,57)
2	4 (12,1)	1 (7,14)
< 2	0 (0)	0 (0)
Cognitive Function	**Morphine 6 - 12 months**	**Morphine for more than 12 months**
	N%	N%
Recall Score		
3	28 (84,8)	10 (71,42)
2	5 (15,1)	2 (14,28)
1	0 (0)	2 (14,28)
Language Score		
9	19 (57,6)	5 (35,71)
8	9 (27,3)	5 (35,71)
7	5 (15,1)	3 (21,42)
6	0 (0)	0 (0)
5	0 (0)	1 (7,14)
<5	0 (0)	0 (0)

Correlation Between Longterm use of Morphine and Cognitive Function

The classification of the longterm use of morphine is presented in **Table 4**, with researchers categorizing patients into two groups based on their chronic pain and longterm use of morphine, extending beyond six months. The first group encompassed individuals with a longterm of use ranging from 6 to 12 months, while the second group consisted of those with a longterm of use exceeding 12 months. The results indicated that the first group (6-12 months) comprised 33 individuals (70.2%), while the second group (more than 12 months) included 14 individuals (29.8%).

In terms of the Mini Mental State Examination (MMSE) scores, the first group (6-12 months) exhibited scores ranging from a minimum of 22 (categorized as probable cognitive impairment) to a maximum of 30 (categorized as normal), with a median value of 29, indicating a normal cognitive status. Conversely, the second group (more than 12 months) demonstrated MMSE scores ranging from a minimum of 23 (probable cognitive impairment) to a maximum of 30 (normal), with a median value of 26. Notably, the median value in the second group was lower than that of the first group, although it remained within the normal range.

Based on these findings, it can be interpreted that there is no significant correlation between the longterm use of morphine and cognitive function among cervical cancer patients in the Palliative Care Clinic of Dr. Soetomo Surabaya Hospital. This interpretation is supported by the Chi-Square test result, which yielded a p-value > 0.05, specifically 0.572.

Table (4) Relationship between longterm use of morphine and cognitive function

Longterm use of morphine	**MMSE Score**				**p**
	N (%)	**Minimum**	**Maximum**	**Median**	
6- 12 Month	33 (70,2)	22	30	29,00	
> 12 Month	14 (29,8)	23	30	26,00	**0,572**
Total	47	22	30	27,00	

Correlation of Morphine Dose with Cognitive Function

We categorized morphine doses into five groups based on their usage at the Palliative Care Clinic of Dr. Soetomo Hospital in Surabaya. In the group receiving a morphine dose of 4 x 2.5 mg/day, the minimum Mini Mental State Examination (MMSE) score observed was 22, the maximum score was 30, and the median score was 27. Similarly, in the group administered a morphine dose of 4 x 5 mg/day, the MMSE scores ranged from a minimum of 23 to a maximum of 30, with a median score of 29. For the group receiving a morphine dose of 4 x 7.5 mg/day, the MMSE scores varied from a minimum of 24 to a maximum of 30, with a median score of 28.

Subsequently, in the group receiving a dose of morphine at 6 x 2.5 mg/day, the minimum MMSE score recorded was 28, with no variation in the maximum score (28) and a median score of 28. Finally, the morphine dose group of 6 x 5 mg/day exhibited a minimum MMSE score of 26, a maximum score of 27, and a median score of 26.5.

Upon conducting a Spearman correlation test, it was determined that there was no significant correlation

between the administered morphine dose and cognitive function. This conclusion is substantiated by a p-value > 0.05, specifically 0.094, and a correlation coefficient of 0.247.

Table (5) Relationship between morphine dose and cognitive function

Morphine Dosage	MMSE Score				r	p
	N (%)	Minimum	Maximum	Median		
4 x 2,5 mg/day	17	22	30	27,00	**0,247**	**0,094**
4 x 5 mg/day	22	23	30	29,00		
4 x 7,5 mg/day	5	24	30	28,00		
6 x 2,5 mg/day	1	28	28	28,00		
6 x 5 mg/day	2	26	27	26,50		
Total	47	22	30	27,00		

DISCUSSION

Characteristics of Research Subjects

In our pursuit of enhancing the well-being of cervical cancer patients, we conducted a study at the Palliative Care Clinic of Dr. Soetomo Hospital in Surabaya, involving 47 participants diagnosed with cervical cancer. This study comprehensively recorded various characteristics, including age, cancer stage, education level, and morphine dosage. The findings of our study reveal that the majority of patients were at stage 3 of cervical cancer, indicating that a significant number of individuals seeking care at the Palliative Care Clinic in Dr. Soetomo Surabaya Hospital were already at an advanced stage of the disease.

The observed predominance of patients at stage 3 is consistent with previous research conducted in Surabaya. A study by Achmadi and Suhatno (2011) on the characteristics and survival rates of cervical cancer patients at Dr. Soetomo Surabaya Hospital between 2006 and 2010 similarly found that the majority of patients were at stages 2B and 3B. Additionally, Rozi et al. (2017) confirmed that the most common clinical stage for cervical cancer patients at Dr. Soetomo Surabaya Hospital during January to December 2017 was stage 3b.

These findings align with retrospective research conducted by Pradikasari (2022) at RSI Jemursari Surabaya, covering the period from 2016 to 2021. This study, focusing on patients with cervical cancer, reported that the majority of patients diagnosed with cervical cancer at RSI Jemursari Surabaya were in stage 3, comprising 35 patients.

Cervical cancer often remains asymptomatic during its precancerous stages. As the disease progresses into invasive cancer, common symptoms include bleeding (particularly during contact or intercourse) and abnormal vaginal discharge. In advanced stages, symptoms can escalate to include lower back or lower abdominal pain due to the tumor's lateral pressure within the pelvic region, leading to ureteral obstruction and potentially oliguria or anuria. Additional symptoms may arise as the tumor infiltrates nearby organs, such as vesicovaginal fistulas, rectovaginal fistulas, and leg edema (Kementerian Kesehatan Republik Indonesia, 2016).

Patients meeting the inclusion criteria encompassed individuals aged 18 to 64 years. The lower age limit of 18 is established in accordance with Indonesian Law No. 12 of 2006, which designates the age of adulthood at 18 years, signifying that individuals of this age are considered capable of making independent decisions. Geriatric patients, on the other hand, are defined as those aged 65 years and above (Cassel et al., 2003). Notably, a study by Bikbov et al. (2021) found that lower Mini-Mental State Examination (MMSE) scores were associated with older age, rural residence, lower educational attainment, higher depression scores, visual and hearing impairments, and reduced physical activity. Consequently, we excluded individuals aged 65 years and older from the study sample.

According to our findings, the median age of patients in this study was 55 years, with the youngest participant being 28 years old and the oldest 64 years, yielding a mean age of 51.96 years. It's worth noting that cervical cancer can manifest symptoms as early as 28 years of age, prompting patients to seek treatment classified as chronic pain and necessitating therapy with morphine and adjuvants. Interestingly, this particular patient exhibited a normal cognitive score.

Previous research by Rozi in 2017 at the Obstetrics and Gynecology Department of Dr. Soetomo Surabaya Hospital aligns with the age demographics of cervical cancer patients, particularly in the Surabaya region. This study revealed that the largest age group among cervical cancer patients was the 51-60 year age bracket, comprising 38.2% of cases (Rozi et al., 2017). In contrast, a study by (Achmadi & Suhatno, 2011) conducted in the oncology department and obstetrics and gynecology inpatient wards of Dr. Soetomo Surabaya Hospital found that the highest age group was 40-49 years, with the youngest patient at 23 years and the oldest at 90 years. Additionally, research at Soedarso Pontianak Hospital for the period 2017-2019 identified cervical cancer cases beginning at the age of 27 years, with a peak incidence

occurring in the 41-60 year age range, where the average age was 48.7 years. The oldest recorded age for cervical cancer was 78 years (Pratiwi et al., 2022).

Cognitive function should not solely be assessed based on the patient's underlying disease, complications stemming from the cancer itself, or the therapeutic interventions employed. Understanding a patient's educational background is equally critical. This approach allows for more specific patient categorization and helps mitigate biases in research outcomes. In our data collection at the Palliative Care Clinic of Dr. Soetomo Hospital, we identified five distinct education levels, alongside a category for those without any formal schooling.

Our study yielded some intriguing insights into the relationship between education level and patients' cognitive function. Notably, none of the patients in our research sample fell into the category of definite cognitive impairment. Instead, all patients categorized as having probable cognitive impairment had educational backgrounds ranging from no formal schooling to completion of elementary school.

Research by (Cano-López et al., 2021), which analyzed data from The National Social Life, Health, and Aging Project (NSHAP), emphasized that higher levels of education were correlated with improved cognitive function and increased functional independence over a 10-year span, irrespective of depressive symptoms (Cano-López et al., 2021).

Beyond the direct influence of cognitive ability linked to education, the experiences acquired during one's educational journey can also significantly impact cognitive functioning. While formal schooling represents not merely a physical space but rather an environment that, on average, provides enhanced cognitive stimulation and opportunities for knowledge and skill acquisition compared to other activities. Schools have the explicit goal of imparting declarative and procedural knowledge, fostering cognitive abilities that can be practiced and acquired. This accumulation of knowledge extends to thinking abilities such as memory and reasoning, ultimately enhancing cognitive strategies and skills (Lövdén et al., 2020).

Another study sought to explore the relationship between educational attainment and cognitive ability, employing online test data with computerized scoring. The study involved participants aged between 15 to 60 years residing in the United States (n = 152,694), Canada (n = 21,767), and Australia (n = 21,927). Findings from this study indicated a connection between educational level and thinking ability across different age groups, although it had little impact on learning effectiveness. These results, while statistically significant and accounting for various confounding factors, demonstrated that education level explained only a small portion of the observed variation. In smaller-scale studies, this effect may not be detectable. Nonetheless, these findings support the notion that higher education offers opportunities to enhance general thinking skills (Guerra-Carrillo et al., 2017).

Our study also incorporated steroid therapy as an exclusion criterion due to its potential influence on cognitive function. Research conducted by Wang et al. in 2019 involved a meta-analysis to investigate the effects of corticosteroids on various cognitive function domains. This analysis revealed that corticosteroids had moderate negative effects on executive function among acute users, impacted current memory in short-term and chronic users, and influenced very longterm memory among acute users (Wang et al., 2019). Additionally, Wang et al. (2019) reported a small yet significant positive effect of corticosteroids on expressive language in short-term users.

Moreover, an article authored by (Bückström et al., 2008), which delves into the influence of neuroactive steroids on cognitive function, particularly focusing on the serotonin and GABA systems, posits that neuroactive steroids are compounds capable of modulating the activity of GABA and serotonin receptors in the brain. These receptors are known to play vital roles in learning and memory processes. The article also addresses factors impacting neuroactive steroid levels, such as stress, pregnancy, menopause, and neurodegenerative diseases. It suggests that neuroactive steroids exert multiple effects on cognitive function, contingent upon factors like type, dosage, longterm use, and target steroid receptors. This article posits that the regulation of neuroactive steroids could serve as a potential therapeutic approach for cognitive disorders (Bückström et al., 2008).

Pain Scale Analysis of Cervical Cancer Patients

According to the results of research at Soetomo Surabaya Hospital, Palliative Care Clinic specialists found that there were 3 patients with no pain, 26 patients with mild pain, 15 patients with moderate pain, and 3 patients with severe pain. Based on these findings, it is evident that cervical cancer patients with mild pain are the most prevalent group (comprising more than 50% of cases), followed by patients experiencing moderate and severe pain. The number of patients with no pain is relatively equal to those with severe pain.

A cross-sectional study, assessing the health-related quality of life (HRQOL) of cervical cancer patients in Indonesia using the EQ-5D-3L questionnaire, revealed that the most common HRQOL problems experienced by these patients were pain or discomfort and anxiety or depression. Additionally, this study demonstrated variations in HRQOL based on cancer stage (Sari et al., 2015).

Another study, which examined symptoms and interventions in palliative care for 88 women with advanced cervical cancer, found that 96% of participants reported pain as the predominant symptom, followed by emotional distress, anorexia, fatigue, insomnia, and constipation at the time of referral to Palliative Care (Kim et al., 2015).

An intriguing study measured the quality of life of women undergoing chemoradiotherapy for cervical cancer. This investigation assessed changes in quality of life before and after chemoradiotherapy treatment among cervical cancer patients. A total of 67 women with newly diagnosed advanced cervical cancer (stage 2b to 4b) participated in this cross-sectional study. The EORTC QLQC30 and EORTC QLQCX24 questionnaires were employed to gauge quality of life. The results indicated that the mean age of women at the time of cervical cancer diagnosis was 52.3 years. Notably, physical, cognitive, and emotional functioning improved significantly after treatment, while symptoms such as fatigue, pain, insomnia, and loss of appetite diminished. However, there was an increase in diarrhea after treatment. To further enhance the quality of life for these patients, interventions that focus on social and psychological support, as well as physical rehabilitation, may be required (Bachani et al., 2016).

Pain perception is highly individualized and influenced by various factors, including cognitive and emotional processes in the brain. The interplay between afferent nociceptive signals from the body and a descending modulator system responsive to cognitive and emotional factors contributes to this diversity in pain experiences. Brain regions involved in this modulator system not only influence pain perception but also play vital roles in overall cognitive and emotional functioning. Consequently, alterations in the structure and function of these brain regions can lead to cognitive impairments, anxiety, and depression in individuals with chronic pain. While establishing the exact temporal relationship between pain, cognitive deficits, and emotional conditions in chronic pain patients is challenging, studies with animals suggest that cognitive and emotional changes can manifest months after the onset of pain, often accompanied by structural brain alterations. This growing body of evidence underscores how chronic pain can have a detrimental impact on the brain, potentially giving rise to multiple coexisting conditions that significantly affect individuals coping with chronic pain (Bushnell et al., 2013).

Furthermore, chronic pain's impact on memory is a significant concern, as some studies indicate that persistent pain can impair memory function. It can make it easier to forget newly acquired information or previously stored knowledge while intensifying the recall of painful memories and evoking negative emotions. Effective pain management is crucial not only for pain relief but also to prevent memory impairment (Mazza et al., 2018).

In research unrelated to cancer, studies on cognitive function in the context of chronic pain have shown that the nature of the pain condition may influence cognitive effects. Additionally, cognitive impairments associated with pain can be temporary and reversible in specific chronic pain conditions, such as headaches. Therefore, further comparative studies across various chronic pain disorders are needed to determine whether impairments are genuinely linked to pain or influenced by other disease-related factors (Meyer & Rustin, 2000).

A recent study aggregating data from various sources investigated the relationship between chronic pain and cognitive function, utilizing the Mini-Mental State Examination (MMSE) test. The analysis revealed no significant correlation between chronic pain and cognitive decline, even when participants were divided into groups based on MMSE test results (Zhang et al., 2021). This study's findings are expected to contribute valuable insights to future research aiming to understand the causal mechanisms behind pain-related cognitive impairment, potentially leading to innovative interventions to mitigate cognitive deficits. Utilizing pre-clinical animal models, advanced neuroimaging techniques, and translational research approaches will be instrumental in this endeavor. Ultimately, a better understanding of pain-related cognitive dysfunction and its treatment holds promise for improving the outcomes of chronic pain patients (Zhang et al., 2021).

Analysis of the Relationship between Longterm use of Morphine and Cognitive Function in Cervical Cancer Patients

This study was conducted at the Palliative Care Clinic of Dr. Soetomo Surabaya Hospital, focusing on patients diagnosed with cervical cancer. This focus was chosen because Indonesia has a cervical cancer incidence rate of 15.9 per 100,000 population, ranking 83rd out of 185 countries. This rate surpasses the world average of 13.1 per 100,000 population, highlighting the need for enhanced efforts in Indonesia to prevent and detect cervical cancer early ((IARC), International Agency for Research on Cancer, 2023). This study represents a therapeutic effort to understand chronic pain management through longterm use of morphine. It was conducted between July and August 2023, with a total study sample of 47 individuals. The results indicate that there is no discernible relationship between longterm use of morphine for more than 6 months and cognitive function.

Notably, the study revealed that none of the patients fell into the definitive category of cognitive impairment.

Among the patients categorized as probable for cognitive impairment, all were aged between 60 and 64 years, had an education level ranging from no schooling to elementary school, and had used morphine spanning for 6 to 18 months. Additionally, the study identified a patient who had utilized morphine for the longest period, which amounted to 48 months. This patient was 63 years old and had an elementary school education level, yet exhibited normal cognitive function as determined by the Mini-Mental State Examination (MMSE) score. These findings emphasize the rationality of using morphine therapy at the Palliative Care Clinic of Dr. Soetomo Hospital.

Although the results did not statistically support the initial hypothesis, revealing no significant association between longterm use of morphine and cognitive function in cervical cancer patients, data from **Table 4** indicate that subjects who utilized morphine for more than 12 months exhibited lower scores in orientation, attention, calculation, recall, and language compared to subjects who used morphine for 6 to 12 months. This information can serve as evidence for healthcare teams to consistently provide appropriate education, support, and physiotherapy efforts to maintain optimal cognitive function in cancer patients.

Prolonged use of opioids, like morphine, comes with inherent risks, leading to various problems like constipation, diarrhea, sedation, nausea, vomiting, and itching (Benyamin et al., 2008; S. Pask et al., 2020). Despite these drawbacks, opioids remain the top choice for chronic pain relief due to their high effectiveness (Portenoy, 2011). It's important to note that patients on longterm opioid therapy can develop tolerance, requiring higher doses for the same pain relief (Anand et al., 2010). However, increased opioid usage can negatively affect cognitive functions like attention, language, orientation, and psychomotor skills. Therefore, regular assessments of patients on chronic pain medication are crucial to detect subtle cognitive changes (M. Pask et al., 2020). Unfortunately, significant side effects associated with opioids, including addiction, depression, and notably cognitive decline, often go unnoticed (Els et al., 2017).

Both mu and kappa-opioid receptor agonists can disrupt normal cognitive function, causing increased psychomotor impairment, reduced accuracy, and memory problems. Because of this dual impact on pain and cognition, researchers are exploring opioid antagonists as potential enhancers of cognitive function (Jacobson et al., 2018).

According to the National Institute on Drug Abuse (2020), longterm use of opioid, even when prescribed by a physician, can give rise to a range of significant issues. Firstly, individuals may develop tolerance, meaning they require larger or more frequent doses of opioids to achieve the desired effects as time goes on. Secondly, repeated opioid use can lead to dependence, which involves alterations in nerve cell activity and temporary reductions in brain function when the drug is not consumed, resulting in withdrawal reactions upon discontinuation. Moreover, behavioral changes and impaired decision-making can manifest as a consequence of both short-term and longterm use of opioid. Finally, the most severe concern is addiction, characterized by an uncontrollable urge to continue using opioids despite experiencing adverse side effects. Extended opioid use can lead to lasting changes in the brain, potentially resulting in risky behaviors. These findings underscore the need for careful monitoring and management when using opioids for chronic pain conditions.

The Brain Injury Association of America asserts that longterm use of opioid leads to alterations in the frontal brain region, resulting in cognitive impairments—difficulties in thinking. Indeed, brain scans have revealed a reduction in the volume of this brain area. Reports indicate that these cognitive deficits can persist for several years after recovery (Brain Injury Association of America, 2019).

Previous studies, as reviewed by Ersek, have investigated the connection between opioid use and neurocognitive function. They have revealed neurocognitive limitations in several areas, including working memory, attention, and processing speed among individuals using opioids, compared to chronic pain patients not using opioids or healthy controls. However, some other studies have not identified neurocognitive deficits in patients treated with opioids (Ersek et al., 2004).

Furthermore, a distinct study that compared individuals with chronic low back pain to healthy controls discovered that prolonged opioid use could potentially worsen performance on tasks demanding intricate attention, as indicated by the TMT-B ratio. This study, which included a group of chronic pain patients not using opioid analgesics for comparison, revealed that those receiving opioids performed more poorly, implying that there is some evidence supporting opioids' impact on complex attention.

Chronic pain patients on longterm opioid medication (over 3 months) showed decreased performance on a task involving numerical and alphabetic sequences (Trail Making Test-B or TMT-B) compared to average scores. Notably, their abilities in other cognitive areas like psychomotor speed and attention/working memory remained normal. In a study by Kurita and colleagues involving 49 chronic non-cancer pain patients on opioids for at least three months, it aligned with prior research, showing no cognitive impairment in areas like attention, working memory, psychomotor speed, and overall

cognitive function. However, deficits were observed specifically on the Trail Making Test-B, which assesses motor function, attention, and mental flexibility (Kurita et al., 2012).

In addition, a deeper analysis in this study revealed that several factors - including being female, getting older, having lower education and income, receiving lower opioid doses, experiencing fatigue, having shorter sleep duration, and dealing with anxiety and depression - were linked to relative neurocognitive impairment. Some of these factors, like sleep problems, anxiety, and depression, can be addressed through clinical interventions and may guide treatment strategies for chronic pain patients using opioids. Interestingly, poorer neurocognitive performance was associated with lower opioid doses, suggesting that effective management of pain (in this case, with opioid analgesics in this specific patient group) could potentially lead to improved neurocognitive function. This finding contradicts the idea that increasing opioid doses necessarily result in greater neurocognitive impairment, which could be due to opioid-related side effects.

Variability in neurocognitive impairment among chronic pain patients on opioid therapy can be influenced by factors like tolerance to opioids, the effectiveness of pain relief, and negative mood related to opioid treatment. Pinpointing the specific roles of pain and opioids in cognitive deficits, as seen in various studies, is challenging because many studies lacked multiple comparison groups, including chronic pain patients not using painkillers, those using non-opioid painkillers, and those on opioid painkillers. Additionally, not all of these studies followed a longterm approach. Nevertheless, recent research suggests that opioid pain relief may actually improve certain aspects of neurocognition in patients, likely by reducing pain and related emotional distress. In summary, these studies collectively emphasize that cognitive impairments linked to chronic pain should not be oversimplified as solely caused by painkillers (Busse et al., 2018).

Besides cognitive and functional alterations, brain imaging has revealed a reduction in brain volume linked to prolonged opioid use. Even after several years of recovery, individuals with a history of opioid abuse still encounter cognitive problems, indicating enduring dysfunction that cannot be solely attributed to the presence of drugs (Ersche et al., 2006).

Additionally, individuals who misuse opioids frequently struggle with solving complex problems and tend to spend less time collecting information and considering their actions, impacting their decision-making and reasoning skills (Tolomeo et al., 2016). Longterm use of opioid can also result in opioid use disorder and induce changes in the brain that impair cognitive functions, including thinking (Brain Injury Association of America, 2019).

To examine the impact of longterm use of opioid on psychomotor skills, a study involving 144 low back pain patients was conducted (Jamison et al., 2003). They underwent neuropsychological tests before and after being prescribed opioids for pain, with test scores showing significant improvement over time. This suggests that longterm use of oxycodone with acetaminophen or transdermal fentanyl didn't significantly impair cognitive function or psychomotor abilities.

Analysis of the Relationship Between Morphine Dose and Cognitive Function in Cervical Cancer Patients

This study examined the relationship between morphine doses administered in the Palliative Care Clinic of Dr. Soetomo Hospital, which were categorized into five groups: 4x2.5 mg, 4x5 mg, 4x7.5 mg, 6x2.5 mg, and 6x5 mg. However, the results indicated that there was no significant relationship between morphine dose and cognitive function, as determined by the Spearman correlation test. This was evident through a p-value exceeding 0.05 (specifically 0.094) and a correlation coefficient of 0.247.

In this study, morphine was chosen as the representative opioid therapy. The Palliative Care Clinic of Dr. Soetomo Surabaya Hospital employs two types of morphine, namely Morphine Oral Immediate Release (MOIR) and Morphine Sulfate Tablets Sustained-release (MST). All study participants were administered MOIR, alongside consistent adjuvant therapy comprising acetaminophen and amitriptyline. It is noteworthy that patients did not use adjuvant therapies like gabapentin to maintain data homogeneity. This combined therapy approach aims to optimize the necessity for morphine while minimizing the occurrence of severe morphine-related side effects.

The Palliative Care Clinic team at Dr. Soetomo Surabaya Hospital employs a diverse range of strategies to alleviate pain and depression in cancer patients. These strategies encompass psychological interventions, social support, and addressing spiritual concerns. As a result, healthcare providers do not always resort to increasing drug dosages, particularly opioids. Therefore, it is crucial for cancer patients to engage in open discussions with their healthcare teams regarding their pain and other symptoms, ensuring they receive appropriate assistance and support.

The opioid system encompasses four distinct receptor types: mu, delta, kappa, and nociceptin, which are activated by various natural compounds, including endorphins, enkephalins, dynorphins, endomorphins, and nociceptins. Notable drugs like morphine and heroin primarily affect mu-opioid receptors, which have a well-understood mechanism of action and are responsible for both pain relief and euphoric effects associated with

opioid drugs. These mu-opioid receptors are widely distributed in the brain and other parts of the body, with high expression in limbic regions like the basal ganglia, thalamus, and anterior cingulate, as well as moderate expression in cortical areas such as the prefrontal and lateral insular regions. However, it's important to note that equivalent analgesic doses of opioids can have different effects on cognitive function, and simple conversions may not account for the distinct pharmacokinetics of various drugs (Corbett et al., 2006; Calo' et al., 2000; Fichna et al., 2007; Fields & Margolis, 2015; Henriksen & Willoch, 2008).

A study conducted by Pask et al. (2020) systematically reviewed the effects of opioids on cognitive function, quality of life, and depression in older adults dealing with chronic pain, both cancer-related and non-cancer-related. The review encompassed various types of studies and participants aged 65 years and older who used opioids for chronic pain. While the majority of the selected studies reported no significant impact of longterm use of opioid on cognitive abilities, four studies did find mixed effects, with declines observed in attention, language, orientation, psychomotor function, and working/delayed verbal episodic memory. These cognitive deficits were associated with higher opioid doses and the use of additional fast-acting opioids. Notably, changes in cognitive function were mainly observed at higher average daily opioid doses, typically ranging from 120 to 190.7 mg of oral morphine equivalents (S. Pask et al., 2020).

In a subsequent study by Byas-Smith et al. (2005), the effects of opioids on the driving ability and psychomotor performance of chronic pain patients on stable opioid therapy were compared to those of healthy volunteers. The study used road driving methods, obstacle tests, and cognitive assessments to evaluate participants' driving performance and cognitive function. The results indicated that there were no significant differences between the opioid-treated group and the control group in terms of driving errors, speed, and accuracy. The study concluded that chronic pain patients on stable opioid therapy could drive safely without discernible differences from normal drivers. Importantly, the study considered morphine-equivalent daily opioid doses, with an average of 118 mg (median 40 mg) in the chronic pain group, suggesting that even with potent analgesics like morphine, driving ability remained comparable to individuals not using opioids and did not impair cognitive function (Byas-Smith et al., 2005).

A study conducted by Gaertner et al. (Gaertner et al., 2008)) delved into the impact of altering daily opioid doses on cognitive and psychomotor aspects associated with driving among patients suffering from chronic non-cancer pain. This research employed a computerized test methodology to assess the cognitive and psychomotor functions of patients both before and after adjustments in their opioid therapy. The study revealed no significant differences in driving performance between the group using opioids and the control group. Consequently, the study concluded that patients with chronic non-cancer pain, who underwent changes in their daily opioid dosage, did not experience impaired driving ability. The morphine dosage range employed in this study was 30-180 mg/day.

This study sheds light on the use of substantial morphine doses in patients with chronic non-cancer pain for several reasons. Firstly, individuals with chronic non-cancer pain typically exhibit a higher tolerance to opioids compared to those with cancer pain, necessitating larger doses to achieve optimal analgesic effects. Secondly, many chronic non-cancer pain patients experience neuropathic pain, which arises from nervous system damage or dysfunction. Neuropathic pain tends to be more challenging to manage with opioids than nociceptive pain (pain resulting from stimuli damaging tissues), thus requiring higher opioid doses for effective relief. Thirdly, patients with chronic non-cancer pain may contend with various factors that influence their response to opioids, including psychological, social, and environmental factors. These factors can modulate pain perception and expression and affect treatment adherence and satisfaction. Consequently, they may contribute to individual variations in opioid dose requirements among patients with chronic non-cancer pain (Gaertner et al., 2008).

The following Cochrane systematic review assessed the effectiveness and safety of oral morphine in managing cancer pain. It encompassed an analysis of 62 randomized controlled studies involving 4241 participants who used oral morphine in either immediate release (MIR) or modified release (Mm/r) forms. The study's findings indicated that oral morphine proved to be an effective treatment for cancer pain, with no significant differences observed between the MIR and Mm/r forms. Daily doses of oral morphine spanned from 25 mg to 2000 mg. However, side effects were relatively common, with approximately 6% of participants discontinuing treatment due to intolerable side effects such as nausea, vomiting, constipation, and somnolence. The study recommended the importance of individualized morphine dose adjustment and titration, alongside appropriate management of side effects (P.J Wiffen et al., 2013).

Several limitations should be acknowledged in this study. Firstly, data regarding the initial morphine dose were collected through patient interviews and medical records. However, determining the precise initial dosage can be challenging, as many patients are referred from other healthcare facilities and may not recall this information accurately. Secondly, morphine treatment often involves dose adjustments over time, including both reductions and increases. Nonetheless, establishing the longterm use for

which each dosage was administered proved to be a complex task. Furthermore, the management of breakthrough pain, which consists of sudden pain episodes associated with chronic conditions like cancer, can be intricate, especially when reliant on oral medications requiring additional doses. Unfortunately, this study did not include data pertaining to the frequency of breakthrough pain occurrences or the quantity of morphine booster doses administered. These limitations should be considered when interpreting the findings and designing future research in this area.

CONCLUSION

This study's statistical analysis and discussion have yielded several significant conclusions. Firstly, it was observed that the majority of cervical cancer patients in Palliative Care Clinic at Dr. Soeotomo Surabaya Hospital experience mild chronic pain, with 55.3% of individuals falling into this category. Secondly, the study found no evidence to suggest that longterm use of morphine is linked to cognitive impairment in palliative patients at the same hospital. Similarly, the daily dosage of morphine did not exhibit any significant association with cognitive impairment in this patient group.

To build upon these findings, future research endeavors are recommended. Longitudinal studies involving larger cohorts should be conducted, alongside preclinical investigations, to further validate the hypothesis that prolonged morphine or opioid use may impact cognitive function. Additionally, it is imperative to conduct further research comparing the effectiveness of opioids with alternative therapies in preventing cognitive impairment among cervical cancer patients. This broader approach aims to improve the overall quality of life for these patients by identifying the most suitable treatment options.

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Address for Correspondence:
Aji Mustika Ningrum, Specialist-1 Medical Education Program, Anesthesiology and Intensive Therapy Study Program, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Regional General Hospital, Surabaya, Indonesia.
Email: arum.ikyuda@gmail.com