



**ADHERENCE TO GUIDELINES: EVALUATION OF OPIOID USAGE
ACCORDING TO THE WHO STEP LADDER GUIDELINE IN INPATIENT
CANCER PATIENTS**

Eko Adhi Pangarsa*, Budi Setiawan, Damai Santosa, Daniel Rizky, Vina Yunarvika, Catharina Suharti
Division of Hematology and Medical Oncology, Faculty of Medicine, Universitas Diponegoro, Jl. Prof. Soedarto
No.13, Tembalang, Semarang, Central Java 50275, Indonesia

*ekopangarsa90@gmail.com

ABSTRACT

WHO analgesic step-ladder is still the mainstay guideline in managing pain. However, pain in cancer patients developed from a more complex pathomechanism, hence requiring special consideration. This study aimed to compare the visual analog scale (VAS) of opioid and non-opioid analgesia in treating cancer patients and evaluate its rationality with World health organization (WHO) analgesic step-ladder. Method: A single-center, cross-sectional and analytic-descriptive study conducted in our centre. The population of this study comprised all cancer patients receiving analgesic therapy. The sampling technique used was consecutive, involving patients who met the inclusion and exclusion criteria. A total of 62 patients were included in the study as the research sample. Pain level was measured before and between 12 – 24 hours after analgesia, using VAS and divided into mild, moderate, or severe. Analgesic regimens were documented, and the daily opioid dose was presented on milligram morphine equivalent. Statistical analysis was performed to compare the variables before and after analgesia using the Wilcoxon signed-rank test, with a p-value <0.05 considered statistically significant. Result: From 62 patients, 46 subjects were included. Median milligram morphine equivalent was 20 mg (0-60). While the majority of patients experienced mild pain, 13 patients (27.7%) had moderate to severe pain. The most commonly used opioid was intravenous fentanyl, administered to 13 patients (27.7%), with a median morphine equivalent dose of 20 mg/day. Only 1 patient received opioid rationally according to WHO. Both non-opioid and opioid group had significant VAS differences before and after therapy ($p = 0.014$ and $p < 0.001$). In both non-opioid and opioid groups, there were differences of VAS scores in the post-administration of analgesic, but these differences were not statistically significant ($p = 0.885$). Conclusion: The study concludes that, although most analgesics were not administered in accordance with the WHO step-ladder guideline, both opioid and non-opioid analgesics were effective in reducing pain in palliative cancer patients.

Keywords: analgesia; cancer; opioid

How to cite (in APA style)

Pangarsa, E. A., Setiawan, B., Santosa, D., Rizky, D., Yunarvika, V., & Suharti, C. (2025). Adherence to Guidelines: Evaluation of Opioid Usage According to the Who Step Ladder Guideline in Inpatient Cancer Patients. *Indonesian Journal of Global Health Research*, 7(4), 695-604. <https://doi.org/10.37287/ijgchr.v7i4.6343>.

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Although its prevalence had lowered, it is one of the symptoms that heavily burden cancer patients' quality of life, and 1/3 of the patients experiencing moderate to severe pain (Snijders et al., 2023). However, pain treatment often inadequate, with physician focusing on primary treatment. Effective pain management is crucial for improving the quality of life in these patients, often requiring a multidisciplinary approach that includes pharmacological and non-pharmacological interventions (Wantonoro et al., 2021). Cancer pain is different from any other pain, as mainly it is associated by many causes and needs a specialized approach. It is a mix between nociceptive pain and neuropathic pain. Pain caused by the cancer itself are generated from inflammation, ischemia, or compression. (Kapoor et al., 2021) The other type of cancer pain is associated by previous treatment, such as chemotherapy, radiotherapy, or curative surgery. (Mestdagh et al., 2023) Some examples of this therapy-

related pain are chemotherapy-induced peripheral neuropathy, musculoskeletal syndrome associated with aromatase inhibitors, and checkpoint inhibitor-associated rheumatic pain.(Glare et al., 2022) This complex mechanism often leads to more than one type of analgesic to reduce pain, for example using non-steroidal anti-inflammatory drugs combined with antidepressants (as anti-neuropathic pain).

Analgesia used for treating patients can be divided into two categories: opioid and non-opioid analgesia. Opioid substance is one of the pharmacological approaches to pain. It is still the mainstay option for pain medication, because of its high effectiveness in reducing pain, little-to-none ceiling effect, and lack of direct damage on organ function.(Dalal & Bruera, 2019) As opioids work on the central nervous system, opioids also offer a wider range in pain management, compared to other regimens (non-steroidal anti-inflammatory drugs for inflammatory pain, and anti-depressants for neuropathic pain).(James & Williams, 2020) This fits the need in treating cancer pain, with its multi-etiological cause.(Rauenzahn et al., 2017) So, the World Health Organization (WHO) organized a pain step-ladder to combat this, where opioid is used for moderate pain (using weak opioids such as hydrocodone and oxycodone) and severe pain (using more potent opioids like morphine).(Anekar et al., 2023) This step-ladder mainly aims to guide clinician in prescribing adequate but rational analgesia. either undertreatment or overtreatment may arise, leading to significant challenges in patient management, including potential addiction or inadequate pain relief. A study in China reported that in terminal lung cancer patients, the morphine milligram equivalent dose decreased by approximately 45 mg as they approached the last 30 days of life.(Zheng et al., 2024) This study aimed to compare the visual analog scale (VAS) of opioid and non-opioid analgesia in treating cancer patients and evaluate its rationality with WHO analgesic step-ladder.

METHOD

Study Design and Setting

This was a single-center, cross-sectional, and analytic descriptive study conducted at Dr. Kariadi Hospital, Semarang, Indonesia. As our center is one of the main cancer referral centers in the region, we have a relatively stable number of inpatient and outpatient admissions. The ethical committee of Dr. Kariadi General Hospital approved this research under number 16161/EC/KEPK-RSDK/2024.

Study Population

We included all adult cancer patients admitted to the in-hospital ward from 2021-2024 with confirmed cancer and reporting pain. Patients were excluded from the study if they were sedated, had a loss of consciousness, experienced non-cancer-related pain, received interventional pain therapy, or had incomplete records of their pain scale assessments.

Data Collection

Data were extracted from patient medical records, and several variables were recorded. These included demographics and patient characteristics such as age, gender, performance status (using the ECOG scale), primary cancer sites, cancer stage, metastatic sites (if present), and whether a consultation to palliative care had occurred. Pain assessment was conducted daily using the Visual Analogue Scale (VAS), which ranges from 1 to 10. Pain levels were categorized as mild (VAS 1–3), moderate (VAS 4–6), and severe (VAS 7–10). Pain level data were collected both before the administration of analgesics and again between 12 to 24 hours after analgesics were prescribed.

Analgesic Use and Dosage

Analgesic regimens were documented with specific details on the type and dosage of each regimens administered. Opioid doses were converted to morphine milligram equivalent

(MME) doses per day for standardization. Opioid rationality was compared using WHO cancer pain step-ladder

Statistical Analysis

We used SPSS version 26.0 for statistical analysis. The Shapiro-Wilk test was applied to assess normality. Comparative analysis in this study utilized several statistical tests to ensure the validity of the results. The Kruskal-Wallis test was employed for non-parametric data to compare more than two independent groups, making it appropriate for analyzing variables such as performance status or metastatic sites based on pain categories. Additionally, changes in pain levels before and after opioid administration were evaluated using the Wilcoxon test, as the pain data, measured by the VAS, is ordinal and not normally distributed. A p-value of <0.05 was considered statistically significant in all analyses, indicating less than a 5% chance of error, thereby ensuring a high level of confidence in the study's conclusions.

RESULT

A total of 62 adult patients admitted to our hospital ward, 2 patients were admitted to the intensive care unit (ICU) and sedated for intubation; 3 patients did not complain of any pain; 6 patients were later confirmed having benign neoplasm; and 4 patients did not have a complete medical record, so we included 46 patients in our study. (Figure 1)

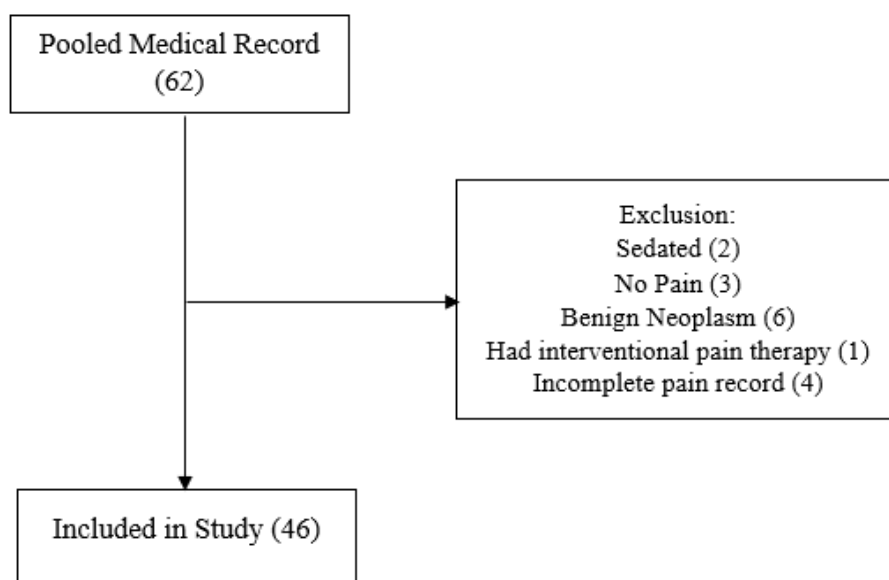


Figure 1. Consort Diagram

Patient Characteristics

Patient Characteristics was shown in Table 1. Most of our patients were female. Twenty patients (42.6%) patients presented with stage IV cancer, and most of patients complaining mild pain. All of our patients were opioid-naïve patients. We compared all of the characteristic variables by baseline. There were no significant differences in baseline VAS scores.

Table 1.
Patient Characteristics

Variable (n=46)		Value	p
Gender (f [%])	Male	15 (34)	0.213*
	Female	31 (66)	
Primary Cancer Site (n)	Breast	11	
	Ovarium	7	
	Thyroid	6	
	Lung	4	
	Colorectal	4	
	Lymphoma	3	
	Liver	2	
	Larynx	2	
	Bladder	2	
	Leukemia	1	
	Endometrium	1	
	Cholangiocarcinoma	1	
	Tongue	1	
	Nasopharynx	1	
	Penis	1	
	Prostate	1	
Sinonasal	1		
Soft Tissue	1		
Brain	1		
Metastasis Location (n)	Lung	5	
	Bone	5	
	Brain	1	
	Peritoneum	1	
	More than 1 site	4	
ECOG Score (n[%])	0	7 (14,9)	0.528^
	1	11 (23,4)	
	2	8 (17,0)	
	3	11 (23,4)	
	4	18 (21,3)	
Palliative consult	Yes	10 (23,4)	0.143*
	No	36 (76,6)	
Age (year)	63,5 (28 – 78)		

*Mann-Whitney Test ^Kruskall Wallis Test

Pain and Opiate Usage

Table 2.
VAS Baseline and Analgesic Regime

Variable		f (%)
VAS (baseline)	Mild	34 (74.0)
	Moderate	11 (24.0)
	Severe	1 (2.0)
Non-Opioid	Other	15 (32.6)
	IV Ketorolac	8 (17.4)
	Oral Paracetamol	5 (10.9)
	IV Paracetamol	2 (4.3)
	Oral Gabapentin	1 (2.2)
	Oral Ibuprofen	2 (4.3)
	Suppository Ketoprofen	1 (2.2)
	IV Ketorolac and Oral Paracetamol	8 (17.4)
	IV Ketorolac and IV Paracetamol	2 (4.3)
	Oral Gabapentin and Oral Diclofenac	1 (2.2)
	Ketoprofen Supp and Oral Mefenamic	1 (2.2)
	Opioid	Other
Oral Morphine		9 (19.6)
Patch Fentanyl		9 (19.6)
IV Fentanyl		13 (28.3)
Codeine		2 (4.2)
Morphine equivalent dose (mg/day)	20 (0 – 60)	

While most of the patients were having mild pain, 13 patients (27,7%) patients having moderate to severe pain. The most used opioid is intravenous fentanyl (13 patients, 27,7%) with a median morphine equivalent dose was 20 mg/day. (Table 2)

Opioid Rationality

Table 3 showed the detailed opioid usage according to the VAS category. Of all of the patients using opioid, only 1 patient were prescribed rational opioid by the doctors, according to the WHO cancer pain stepladder.

Table 3.
VAS Category (Before Analgesia)

		Mild	Moderate	Severe	Total
Opiate Type	No Opiate	12	1	0	13
	Oral Morphine	5	4	0	9
	Patch Fentanyl	6	3	0	9
	IV Fentanyl	9	3	1*	13
	Codeine	2	0	0	2
Total		34	11	1	46

*Rational opioid use

Opioid Use and VAS Difference

Table 4 shows the VAS in the baseline and VAS after analgetic use. The baseline VAS showed a significant difference between patients prescribed with opioids and not given opioids. In both groups, there were significant differences in the post analgetic VAS score, but not statistically significant.

Table 4.
VAS difference in patients given opioid and not given opioid

VAS Score	All Patients (n=46)	Non-Opioid (n=13)	Opioid (n=33)	p*
Baseline VAS (mean ± SD)	3.28 ± 1.09	2.62 ± 0.961	3.55 ± 1.034	0.003
Post Analgetic VAS (mean ± SD)	2.02 ± 1.22	1.92 ± 1.04	2.06 ± 1.30	0.885

*Mann-whitney test

The delta between post-analgetic and baseline VAS in non-opioid and opioid-prescribed patients. There were 6 patients in the non-opioid group and 12 patients in the opioid group whose VAS score did not improve. Both groups showed significant differences in baseline and post-analgetic VAS (table 4).

Table 5.
The VAS difference between post and pre-analgesia in no-opioid and opioid group

Opioid usage	Delta VAS	N (%)	p*
Non-opioid	-2	2 (15.4%)	0.014
	-1	5 (38.5%)	
	0	6 (46.2%)	
Opioid	-7	1 (3.0%)	<0.001
	-4	1 (3.0%)	
	-3	3 (9.1%)	
	-2	13 (39.4%)	
	-1	3 (9.1%)	
	0	12 (36.4%)	

*Wilcoxon Signed-Rank test

We showed the VAS Score in patients referred to palliative care and patients who did not. There was a significant post-analgesic VAS difference between the palliative and non-palliative groups, with a greater VAS reduction observed in patients who were not referred for consultation (table 5).

Table 6.

VAS difference between patients who were given opioids and those who were not, among those referred to palliative care.

VAS Score	All Patients (n=46)	Palliative (n=10)	Non-Palliative (n=36)	p*
Baseline VAS (mean ± SD)	3.28 ± 1.09	3.50 ± 0.707	3.22 ± 1.174	0.274
Post Analgetic VAS (mean ± SD)	2.02 ± 1.22	2.80 ± 1.229	1.8 ± 1.142	0.035

* Mann-whitney test

The VAS difference before and after analgesia in palliative and non-palliative groups. No significant VAS difference after opioid treatment was found in patients admitted to palliative care, compared to the non-palliative group (table 6).

Table 7.

The VAS difference between post and pre analgesia in palliative and non-palliative group

Palliative Referral	Delta VAS	N (%)	p*
Yes	-3	1 (10%)	0.102
	-2	2 (20%)	
	0	7 (70%)	
Total		10 (100%)	
No	-7	1 (2.8%)	<0.001
	-4	1 (2.8%)	
	-3	2 (5.6%)	
	-2	13 (36.1%)	
	-1	8 (22.2%)	
	0	11 (30.6%)	
Total		36 (100%)	

* Wilcoxon Signed-rank test

DISCUSSION

We initially reviewed 62 medical records of patients admitted to our in-hospital ward. During our checking, we excluded 15 patients whom we could not measure the VAS, therefore leaving us with the remaining 46 patients. From all of the patient characteristics, we did not find any significant differences between each characteristic in term of baseline VAS. In this study, we found significant pain reduction in patient receiving opioid or non-opioid analgesic. Looking at other perspective, however, from 34 patients receiving opioid therapy, only 22 of them showing improvement in VAS Score. This means that opioid usage, even given in moderate pain, sometimes did not have effects. The WHO analgesic ladder, has been the main guideline in pain management. However, some studies criticized its use because of the rigid structure and the evolving landscape of cancer pain management. Research indicates that many patients on weak opioids (step 2) experience inadequate pain relief, with over 50% needing to switch to strong opioids (step 3) for effective management. (Ballantyne et al., 2016; Bandieri et al., 2016; M. T. Fallon et al., 2023) This was also shown in our study that strong opioids relieved the pain in most of our cases, either in moderate or severe pain. Although no significant difference is shown in our study, the proportion of patients whose pain had not been alleviated was higher in the non-opioid group. This shows that opioid is still needed for cancer pain. The use of weak opioids in our study (codeine) was mainly for non-pain management. It was also mentioned in a study in India, a low-middle-income country, that weak opioids were significantly costlier than strong opioids, therefore increasing cost with lower effectivity on pain management. (M. T. Fallon et al., 2023) This was also reflected in our study, as physicians preferred to prescribe non-opioid analgesics for mild to moderate pain. Despite the vast variety of non-opioid regimens, its effectiveness is quite comparable to weak opioid in reducing pain. However, these regimens often only managed to lower the VAS Score, not completely eliminating pain. Compared with the side effects, non-opioid analgesic prescriptions, especially for chronic pain, should be closely monitored.

In late-stage cancer, patients are usually referred for palliative care. The main aim for this type of care is to provide symptom relief and a better quality of life. Pain management is also crucial in patients receiving palliative care. In our study, eleven out of twenty patients with stage IV cancer were admitted to palliative care. However, palliative admission was usually done when patients were really at the end-of-life care, with some patients admitted just 1 day before their recorded death. In terms of pain management in these patients, most of our patients who were later admitted to palliative care (70%) did not respond to the pain medications prescribed. This emphasized the need of earlier palliative care admission, therefore giving access to stronger opioid and/or other painkiller medication. The WHO analgesic ladder, has been the main guideline in pain management. However, some studies criticized its use because of the rigid structure and the evolving landscape of cancer pain management. Some studies indicates that many patients on weak opioids (step 2) experience inadequate pain relief, with over 50% needing to switch to strong opioids (step 3) for effective management. (Ballantyne et al., 2016; Bandieri et al., 2016). In a more recent clinical study, low dose morphine (step-3 analgesic) was proven to be superior in alleviating pain compared to weak opioid (M. Fallon et al., 2022). This was also showed in our study that strong opioid relieved the pain in most of our cases, either in moderate or severe pain. Although no significant difference is shown in our study, the proportion of patient whom pain had not alleviated was higher in non-opioid group. This shown that opioid is still needed for cancer pain. The use of weak opioid in our study (codeine) was mainly for non-pain management. It was also worth to mention that in a clinical trial, weak opioid costed higher than low dose morphine, especially in developing country such as Mexico and Uganda.(M. Fallon et al., 2022)

Although opioids is effective in lowering cancer pain, healthcare providers need to be careful in preventing non-medical opioid use (NMOU). Research indicates that nearly one in five cancer patients exhibit behavior indicative of NMOU, highlighting the need for proactive measures such as universal screening tools to identify at-risk individuals early on.(Yennurajalingam et al., 2021) Opioid used in this study, such as fentanyl and morphine and their derivatives contributed in the 10 most abused drugs in 2011 – 2016. Moreover, implementing harm reduction strategies—such as careful monitoring of prescription dosages and encouraging the use of alternative pain management therapies—can significantly enhance patient safety while maintaining effective pain control. A guideline proposed by the European Society of Medical Oncology (ESMO) can be a reference for managing safe and effective opioid administration for cancer pain.(M. Fallon et al., 2018) By fostering an interdisciplinary team environment, which integrates psychological support alongside medical treatment, providers can address the complex nature of pain management and reduce the likelihood of adverse outcomes related to opioid misuse. A comprehensive approach that prioritizes patient education, ongoing assessment, and collaborative care will not only improve the quality of life for cancer patients but also mitigate the risks associated with opioid therapy.

Limitations of this study including the VAS method was mainly subjective, so there might be differences between patient and interpreter. VAS was measured by nurse or physician assistant as one of the nursing assessment, and sometimes were not followed up or documented properly. Another limitation was some patient already receiving fentanyl as one of the post-operative analgesia regiment. This study also did not account about the follow up in post in-hospital visit, therefore limiting the analysis and rationality of the opioid usage. Future studies should consider incorporating objective pain assessment methods and include follow-up visits after hospital discharge to better evaluate the long-term effects and rationality of opioid usage.

CONCLUSION

Our study showed although most analgesics were prescribed not in according of WHO guideline both opioid and non-opioid analgesics were effective in reducing pain in cancer patients. We also found many patients using weak opioids did not achieve adequate pain relief and ultimately required a transition to strong opioids, highlighting the limitations of the guideline. Additionally, delayed referrals to palliative care restricted patients' access to optimal pain management, emphasizing the need for earlier intervention

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