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RESEARCH ARTICLE
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Quinolinic Acid and Chronic Cancer Pain

Fikri Bariz[1*], Christrijogo Sumartono Waloejo[1], Prananda Surya Airlangga[1], Prihatma Kriswidyatomo[1], Budi Utomo[2], Hamzah[1]

[1]Department of Anesthesia and Reanimation, Faculty of Medicine, Airlangga University - Dr Soetomo Hospital, Surabaya, Indonesia.

[2]Department of Public Health Sciences-Preventive Medicine, Faculty of Medicine, Airlangga University, Surabaya, Indonesia.

***Corresponding author:** Fikri Bariz, Department of Anesthesia and Reanimation, Faculty of Medicine, Universitas Airlangga - Dr Soetomo Hospital, Surabaya, Indonesia, Email: barizbaziad@gmail.com

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ABSTRACT

Pain is a complex phenomenon that is influenced by both objective and subjective factors. In patients with cancer undergoing active therapy, the prevalence of chronic pain is estimated to range from 30% to 50%. Given the complex nature of cancer patients' conditions, including impaired physical function, psychological distress, and various other problems, a comprehensive pain assessment is necessary to ensure effective pain management, reduce morbidity, and prevent opioid dependence. Objective measurement of pain is essential to improve the quality of chronic pain services for malignancy, and several biomarkers have been identified as potentially useful tools for measuring chronic pain more objectively. Quinolinic acid is one of these significant biomarkers that have been found to be useful for assessing pain. This study represents the first investigation in Indonesia of the relationship between quinolinic acid and chronic cancer pain. A cross-sectional study was conducted with 85 participants, including 29 male and 56 female patients. The pain scale was measured using the Numerating Rating Scale (NRS) with a range of 0-10, and serum quinolinic acid levels were measured using ELISA. Of the 85 study participants, 29 patients (34.12%) had pelvic organ cancer, 21 patients (24.71%) had head and neck cancer, 12 patients (14.12%) had abdominal organ cancer, 7 patients (8.24%) had breast cancer, 5 patients (5.88%) had pulmonary cancer, 4 patients (4.71%) had skin cancer, and 7 patients (8.24%) had other types of cancer. The study found that the effect of quinolinic acid on the degree of pain was significant ($p = 0.024$), with a correlation coefficient (r) of 0.244. However, the effect of kynurenic acid on the duration of pain was not significant ($p = 0.135$). In conclusion, quinolinic acid was found to be correlated with the degree of pain in chronic cancer patients, but it had no correlation with the duration of pain. Further research is needed to explore the potential of quinolinic acid as a biomarker for chronic pain assessment and management in cancer patients.

Keywords: *Chronic cancer pain, Duration of pain, Pain, Pain scale, Quinolinic acid*

INTRODUCTION

Patients with cancer (malignancy) have a wide range of complaints including impaired physical and psychological functioning, and a variety of problems that can worsen their quality of life (Neufeld et al., 2017). Quality of life (QoL) reflects a complex multifactorial construct, comprising measures of functioning in the physical, social, spiritual and psychological domains (Lawlor et al., 2018).

Pain is one of the main problems that make the quality of life of cancer patients reduced. Pain was reported in 52.2% of patients who had undergone anti-cancer therapy and 74.8% in patients with further treatment due to metastasis. In a journal review, approximately 46% of cancer patients experiencing pain reported moderate to severe levels of pain (Russo & Sundaramurthi, 2019; Van den Beuken-van Everdingen et al., 2007).

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience linked to actual or potential tissue damage (Raja et al., 2020). This definition suggests that pain encompasses both objective components, such as the physiological aspects of pain sensation, and subjective components, such as emotional and psychological factors (Haefeli & Elfering, 2006).

Chronic pain is defined as persistent or intermittent pain that persists over a prolonged period, leading to restricted daily activities, limitations, anxiety, depression, and opioid dependence. Its prevalence worldwide ranges from 8% to 60% (Dahlhamer et al., 2018). Treating chronic pain patients in the United States is estimated to cost between $560-635 million annually, making it more expensive than other diseases such as heart disease, cancer, and diabetes (Phillips, 2009).

Pain assessment is a crucial step that should not be overlooked. Utilizing a cancer pain classification system can aid in understanding the multidimensional nature of cancer pain. Identifying the unique multidimensional aspects of cancer pain in each patient is essential in developing an effective treatment plan. Doing so can optimize quality of life and prevent complications due to uncontrolled cancer pain (Lawlor et al., 2018; Rodriguez et al., 2019)

Poorly controlled pain can have a devastating impact on both patients and their families. The significance of pain management as a routine component of 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 undergoing active therapy for solid tumors and up to 70-90% in those with advanced disease. A prospective survey has shown that simple drug therapy can provide adequate pain relief to approximately 90% of patients, but this success is not commonly achieved in routine practice (Van den Beuken-van Everdingen et al., 2007).

High morbidity, opioid dependence, and the limited efficacy of conventional treatments underscore the need for more objective measures of chronic pain to improve its management and physiological identification. In recent years, several studies have identified potential biomarkers for objective measurement of chronic pain, as opposed to subjective pain scores (Amirdelfan et al., 2020; Gunn et al., 2020). For example, one study found that methylmalonic acid, xanthurenic acid, pyroglutamate, kynurenine, and hydroxymethylglutarate were significant biomarkers for assessing pain ($p<0.005$) (Amirdelfan et al., 2020).

On the other hand, in another study, quinolinic acid (29%) and kynurenic acid (27%) were the most common abnormal biomarkers among 17,834 patients examined. Both are detectable biomarkers of chronic inflammation mediated by inflammatory cytokines (Gunn et al., 2020).

Quinolinic acid is a pyridine compound that belongs to the 2,3-dicarboxylic acid family. It acts as an NMDA receptor agonist, binding to the NR2A and NR2B subunits. It is also one of the biomarkers used to measure chronic inflammatory processes in the kynurenine pathway. Chronic inflammation mediated by inflammatory cytokines in this pathway is known to cause pain. Recent studies have revealed how cytokines play a role in the chronic pain process, and the kynurenine pathway associated with tryptophan, an amino acid in this process,

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contributes to the production of cytokines significant in the incidence of chronic pain (Walczak et al., 2020). In this context, the relationship between quinolinic acid levels and the degree and duration of chronic pain in cancer patients is being investigated.

MATERIAL AND METHODS

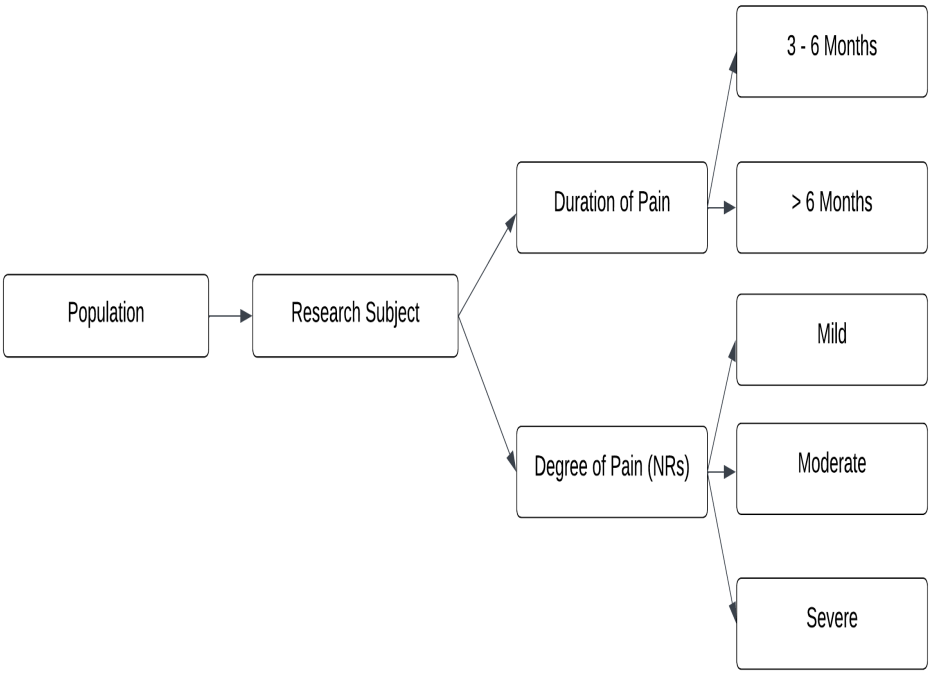

FIGURE 2-1.: "Research design"

The research design of this study was analytical observational research with a cross-sectional design. The study was conducted at the Palliative Clinic of Dr. Soetomo Hospital until the sample size was met. The study population consisted of patients with cancer in the Palliative Clinic who had chronic pain. Patients who met the inclusion criteria, such as having a malignancy underlying disease, age between 21-65 years, and being able to communicate well, were included in the study. Patients who refused to participate, had severe infectious disorders, blood disorders, or were using steroid therapy, were excluded from the study. The sampling technique used was consecutive random sampling, and the sample size needed was 87 patients. The research instruments used were the medical record, quinolinic acid level, and the NRS diagram. The research procedure included obtaining informed consent from patients and families, with explanations delivered in layman's language, and patients and families were not charged for the study. If pain arose during the study, treatment was provided in accordance with medical service standards in the palliative clinic.

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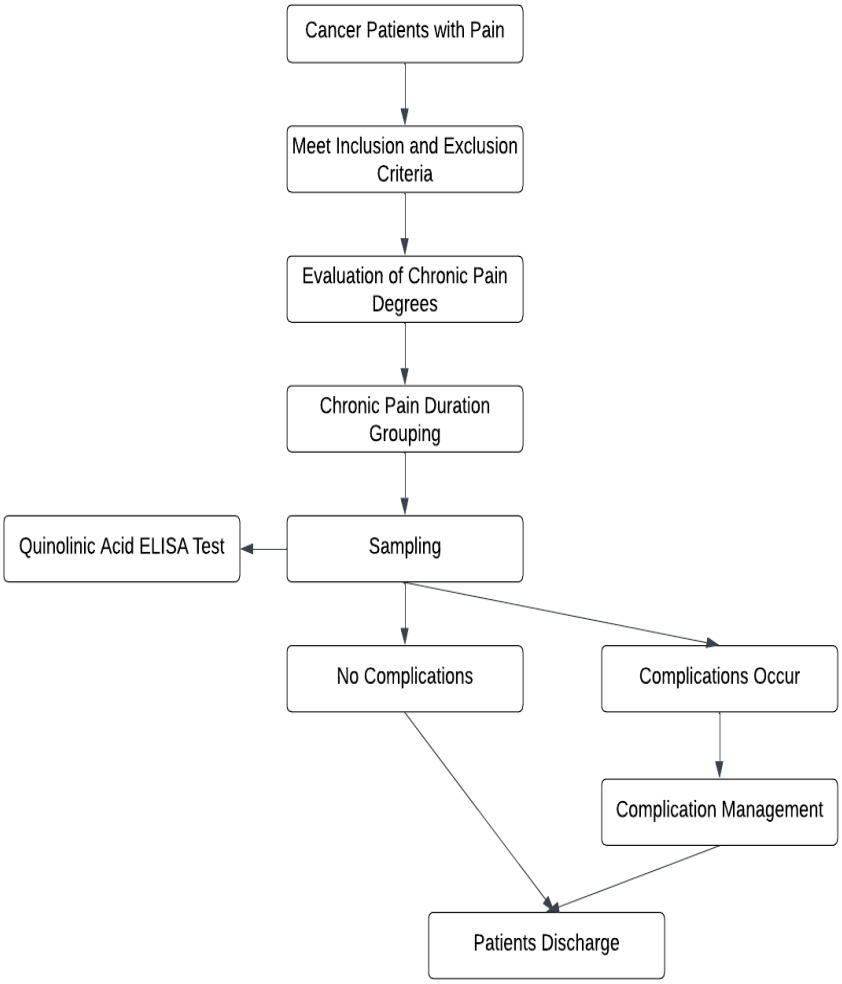

FIGURE 2-2.: "Operational framework"

Data that was collected was recorded and tabulated, and data processing in this study used the Jamovi application version 2.3.21. All data was summarised using descriptive statistics: mean and standard deviation for quantitative (numerical) values, and number and percentage for categorical data. To analyze the effect of blood quinolinic acid levels on the degree of chronic pain in cancer patients, the Pearson test was used for normal data distribution, and Spearman test was used for abnormal data distribution. A value of $p<0.05$ was considered statistically significant. For the analysis of the effect of blood quinolinic acid levels on the duration of chronic pain in cancer patients, the Pearson test was used for normal data distribution, and the Spearman test was used for abnormal data distribution. A value of $p<0.05$ was considered statistically significant.

RESULT

Characteristics of the Research Subject

This study involved 85 patients who met the inclusion and exclusion criteria from the Palliative Clinic of Dr Soetomo Hospital Surabaya. The research subjects were patients with cancer, with the frequency of pelvic organ cancer being 29 people (34.12%), head and neck cancer 21 people (24.71%), abdominal cancer 12 people (14.12%), breast cancer 7 people (8.24%), lung cancer 5 people (5.88%), skin cancer 4 people (4.71%), and other cancers 7 people (8.24%).

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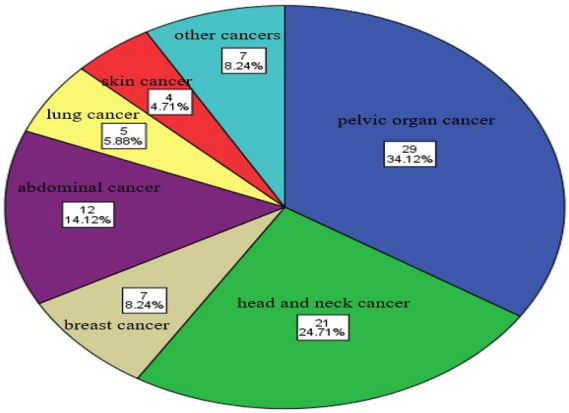

FIGURE 3-1.: "Distribution of patients by type of malignancy"

Based on the normality test, none of the patient characteristics in this study were normally distributed (p>0.05). The characteristics of patients in this study are summarised in table 1 where the mean age of patients in this study was 53 years (youngest age 21 years and oldest age 65 years). Most of the subjects in this study were female, with 56 people (65.9%).

Based on the classification of chronic pain duration, most patients had symptoms lasting more than 6 months (68.2%), with the majority of patients experiencing mild pain (50.6%). The results of the quinolinic acid examination showed a mean value of 244.2 ng/L with the lowest value of 20 ng/L and the highest value of 4,286 ng/L.

The NRS pain scale was used in this study to measure the degree of pain in patients. The NRS pain scale is calculated using numbers 0-10. The most common pain scale value obtained was 2, with 19 patients (22.4%), while the least common pain scale values were 0 and 9, with 0 patients (0%).

Based on grouping by the degree of pain, namely mild, moderate, and severe, the data showed that 43 people had mild pain (50.6%), 33 people had moderate pain (38.8%), and 9 people had severe pain (10.6%). These characteristics are presented in table 1.

This study found that most patients with pain symptoms lasting between 3-6 months experienced moderate pain (55.6%), while patients with pain symptoms lasting more than 6 months mostly experienced mild pain (58.6%).

TABLE 3-1.: "Characteristics of the subject of study"

Variable	Mean + SD	Median (Min-max value)	N (%)	p* value
Age (years)		53 (21-65)		
Gender Man Woman			 29(34,1) 56(65,9)	
Duration of chronic pain 3-6 months > 6 months			 27 (31,8) 58 (68,2)	<0,001
Degree of Pain Mild Moderate Severe			 43(50,6) 33(38,8) 9 (10,6)	<0,001
NRS Pain Scale 0 1			 0(0) 9(10,6)	<0,001

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2 3 4 5 6 7 8 9 10			19(22,4) 15(17,6) 13(15,3) 10(11,8) 10(11,8) 5(5,9) 3(3,5) 0(0) 1(1,2)	
Quinolinic Acid Levels (ng/L)	244,2 (±524,49)	116 (20-4.286)		<0,001

*Kolmogorov-Smirnov data normality test

TABLE 3-2.: "Degrees of pain by duration of chronic pain"

Duration of chronic pain	Degree of pain			p* value
	Mild	Moderate	Severe	
3-6 months > 6 months	9 (33,3%) 34 (58,6%)	15 (55,6%) 18 (31,0%)	3 (11,1%) 6 (10,3%)	0,059

*Mann-Whitney difference test

Relationship of Research Subject Characteristics with Quinolinic Acid Levels

In this study, there was no significant relationship found between age, gender, and cancer type with quinolinic acid levels. The contingency coefficient test showed that the difference in quinolinic acid levels based on age had a value of p=0,522.

The Mann-Whitney test results indicated that the difference in quinolinic acid levels between male and female patients was not statistically significant (p=0,717), although the mean quinolinic acid levels in men (296,21 ±775,5 ng/L) were higher than those in women (217,27 ±334,3 ng/L).

Moreover, based on the results of the Kruskal-Wallis test, the difference in quinolinic acid levels among cancer types was not statistically significant (p=0.540), although lung cancer patients had a higher mean value of quinolinic acid levels (963,8 ±1.859,094 ng/L) compared to other types of cancer.

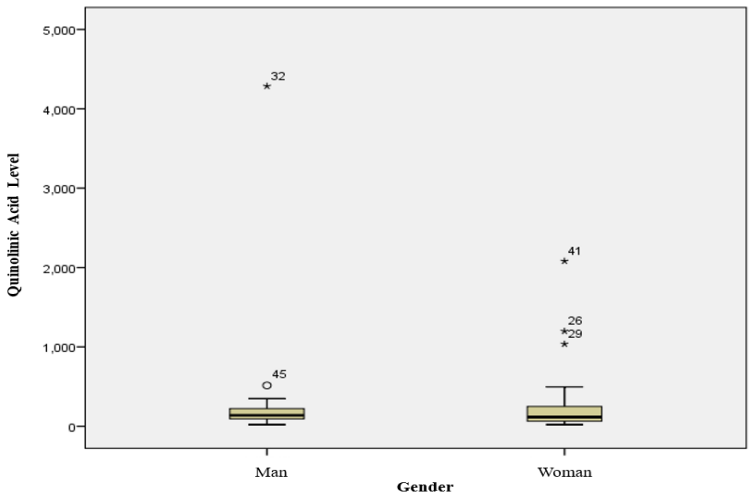

FIGURE 3-4.: "Box plot of gender with quinolinic acid levels"

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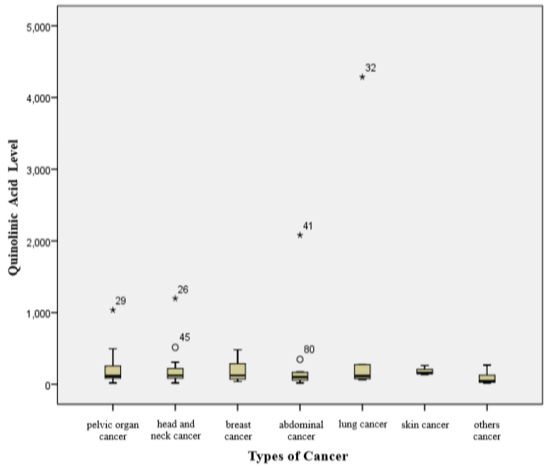

FIGURE 3-5.: "Box plot of quinolinic acid levels and cancer types"

Correlation of Quinolinic Acid Levels with Duration and Degree of Pain

Spearman's correlation test showed no significant correlation between chronic pain duration and quinolinic acid levels (p=0.135). However, a significant relationship was found between the degree of pain measured by the NRS scale and quinolinic acid levels (p=0.024). The correlation coefficient r=0.244 indicated a weak positive correlation between the degree of pain and quinolinic acid levels, suggesting that higher pain levels were associated with higher levels of quinolinic acid.

TABLE 3-3.: "Correlation of quinolinic acid levels with duration and degree of pain"

Variable	Kynurenine levels Average ±SD (ng/L)	P value	R value
Duration of chronic pain		0,135	-0,163
3-6 months	235,78 ±274,452		
> 6 months	248,12 ±609,093		
Degree of pain		0,047	0,216
Mild	189,37 ±326,273		
Moderate	212,45 ±251,761		
Severe	622,56 ±1.376,482		
NRS pain scale		0,024	0,244

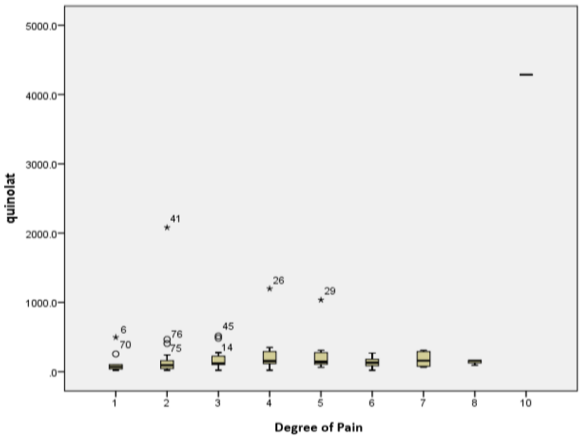

FIGURE 3-6.: "Box plotting quinolinic acid levels and NRS pain scale"

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DISCUSSION

Characteristics of the Research Subject

In this study, 85 patients with malignancies who experienced chronic pain were included, with the three largest groups being pelvic organ cancer (29 people or 34.12%), head and neck cancer (21 people or 24.71%), and abdominal cancer (12 people or 14.12%), with a female dominance of 56 patients (65.9%).

This study is the first to analyze the relationship between quinolinic acid levels and chronic pain in cancer patients. In Gunn et al.'s study, a retrospective analysis of quinolinic acid levels was conducted in more than 17,000 patients with chronic pain, with 29% of subjects having abnormal results. However, there is no detailed mention of the demographic data of chronic pain patients studied, so this study cannot discuss differences in demographic characteristics with previously conducted studies.

This study found that quinolinic acid levels in men (296.21 ± 775.5 ng/L) were higher than in women (217.27 ± 334.3 ng/L). This study is in line with the research of Verma et al. (Verma et al., 2022), where the mean serum level of quinolinic acid in healthy men (33.88 ± 2.787) was higher than in healthy women (26.18 ± 1.407) with a significance of p=0.0216.

However, this study used samples of healthy individuals, and the higher level of quinolinic acid in men may be due to the neuroprotective factor of estrogen in women, which causes less production of quinolinic acid (Heron & Daya, 2001).

This study found four subjects with quinolinic acid levels above 1000 ng/L, with different types of cancer. Two subjects had a pain duration of 3-6 months, and the other two subjects had a pain duration of over 6 months. In subjects with quinolinic acid values above 2000 ng/L, both had the same characteristics, namely pain duration of over 6 months. This finding suggests that pain duration may be related to quinolinic acid levels and can be a further area of investigation to remove biases such as psychological factors and the determination of when a patient's pain is considered significant.

Relationship of Quinolinic Acid Levels and Pain Duration

The results of this study showed that 68.2% of patients had chronic pain lasting for more than 6 months. Spearman's correlation test revealed an insignificant correlation between quinolinic acid levels and pain duration (p=0.135). As there is no comparative study analyzing the relationship between quinolinic acid levels and chronic pain duration, no comparison with other studies can be made.

Research by Gunn et al. (Gunn et al., 2020) found that the average blood quinolinic acid level in chronic pain patients was 5.6 ±µg/mg creatinine, with 29% prevalence of abnormal quinolinic acid levels. This suggests that quinolinic acid plays a role in the chronic pain pathway. The kynurenine pathway will increase the production of quinolinic acid, which is a metabolite of kynurenine, in systemic inflammatory responses. As a result, it can be a sensitive biomarker of systemic inflammation in chronic pain. The mechanism that can influence the process is that the kynurenine pathway increases in this regulation due to a decrease in serotonin, where both pathways use tryptophan as their initial substrate.

Decreased serotonin levels not only cause depression but can also decrease the activity of the descending inhibitory pain pathway, resulting in an increase in the degree of pain even when serotonin levels are normal. The upregulation of the Kynurenine pathway, assisted by enzymes IDO-1, IDO-2, and TDO, can affect serotonin levels. IDO1 plasma levels have been found to increase in patients with chronic pain compared to normal patients (Kim et al., 2012). Moreover, other derivatives of the kynurenine pathway, such as kynurenic acid, have also been observed to have abnormal changes in value in patients with chronic pain. Abnormal results were obtained in kynurenic acid levels in the blood and urine of chronic pain patients with a prevalence of 27% and 33%, respectively, in studies by Gunn et al. (Gunn et al., 2020) in 2020 and Pope et al. (Pope et al., 2021) in 2021.

Pain in cancer patients can last a long time due to the pathophysiological process itself. If not managed properly, it can decrease the patient's

quality of life and affect the treatment process. Breakthrough pain in cancer patients who have received controlled chronic pain therapy can be a bias in this study. Therefore, no significant relationship was found between pain duration and quinolinic acid levels.

Chronic pain that persists for a prolonged period has the potential to cause depressive disorders in patients. Poorly managed pain can increase the risk of developing depression. Quinolinates have been associated with impaired cognitive function tests and major depressive disorder (Anderson et al., 2021; Paul et al., 2022).

Currently, there is no standardized benchmark for the duration of chronic pain, other than when it is felt for three months or more. However, one study suggests that raising the cutoff for chronic pain to six months can reduce the estimated prevalence by 30% (Sá et al., 2019). This could be a useful point of reference for further research into the duration of chronic pain.

Relationship between Quinolinic Acid Level and Pain Intensity

In this study, pain intensity was measured using the Numeric Rating Scale (NRS) and classified into mild, moderate, and severe categories. Of the 85 patients analyzed, 43 had mild pain (50.6%), 33 had moderate pain (38.8%), and 9 had severe pain (10.6%). The data analysis revealed a significant association between quinolinic acid levels and pain intensity measured using the NRS scale ($p=0.024$). These findings are consistent with previous research that reported abnormal quinolinic acid levels in patients with chronic pain (Gunn et al., 2020; Pope et al., 2021). However, those studies did not classify pain intensity.

The correlation coefficient was 0.244, indicating a weak relationship between quinolinic acid levels and pain intensity. The positive r value suggests that higher pain intensity is associated with higher quinolinic acid levels, which is consistent with the mechanism of quinolinic acid formation. The kynurenine pathway is activated from tryptophan when inflammation occurs. However, there are no other studies available to compare the results of this study regarding the relationship between quinolinic acid levels and chronic pain in cancer patients.

The results of this study support the theory that there is a link between quinolinic acid and chronic pain in cancer patients. There are several factors that could be further researched in relation to this, such as depression, mood, and anxiety levels in cancer patients with chronic pain. Depression and anxiety have been found to affect quinolinic acid levels, as shown in studies by Steiner et al. (2011) and Athnaiel et al. (2022), which found an association between depression and quinolinic acid levels in the brain.

Furthermore, the relationship between quinolinic acid levels in the blood and urine could also be explored further, as abnormal values have been found in both in different studies (29% in blood and 33% in urine) (Gunn et al., 2020; Pope et al., 2021). This finding could form the basis for research into the relationship between quinolinic acid levels and chronic pain. Other biomarker studies have shown an association between chronic pain and other biomarkers. For example, Waloejo et al. (2022) found a negative correlation between kynurenine acid levels and the degree of pain, with a p-value of 0.043. This suggests that the higher the degree of pain, the lower the kynurenine acid levels in the blood. This study could provide a guide for comparing the levels of both biomarkers and offer new insights into chronic pain management in cancer patients.

The immune response can lead to an increase in the activity of the enzyme IDO-1, which activates the kynurenine pathway, resulting in increased quinolinic acid levels. Inflammatory conditions in the brain can lead to the infiltration of macrophages, microglia, and dendritic cells, which are the largest sources of quinolinic acid production. Increased concentrations of quinolinic acid have been found in cerebrospinal fluid in neurodegenerative diseases and experimental animal studies, suggesting that quinolinic acid plays a role in the pain modulation process related to neurodegenerative diseases and inflammation (Davis & Liu, 2015).

This study sheds light on the association between quinolinic acid and chronic pain in cancer patients, which can help in the pain assessment

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and management of cancer patients. Cancer pain is a significant concern for cancer patients, and the existence of biomarkers that provide an objective picture of cancer pain can aid in patient management and clinical health services. Periodic screening of patients with chronic pain can help determine more comprehensive management and guide when to switch to other therapies or pain management measures. This can reduce patients' time in pain and allow healthcare centers to make more efficient use of available resources.

The results of this study can provide insights into further research for the development of therapy for cancer patients with chronic pain. It is suggested that a decrease in quinolinic acid levels may help reduce the degree of pain in cancer patients since an increase in quinolinic acid levels was found to be associated with an increase in pain degree. If the degree of pain in cancer patients is reduced, their quality of life can improve, and they can carry out their daily activities better.

The relationship between the quality of life and metabolites of kynurenine can be further investigated, given that kynurenic acid (KYNA) and quinolinic acid (QUIN) have a relationship with the degree of chronic pain in cancer patients. However, this needs to be confirmed with further research.

This study has several limitations that cannot be avoided, including the fact that pain was only assessed at one point, namely when the patient comes to the Palliative Clinic. Therefore, the overall pain picture of the patients has not been fully obtained, which may affect the quinolinic acid levels. Future research can consider assessing pain using a more comprehensive scale, such as the Brief Pain Inventory, to capture more complex pain experiences.

Moreover, this study was conducted only in one healthcare center, which may limit its generalizability to the wider population. Therefore, future studies on a larger scale are needed to obtain more representative results. Additionally, no other markers related to the kynurenine pathway or inflammatory mediators were examined in this study. Further research is needed to explore the relationship between inflammation and the kynurenine pathway in cancer patients with chronic pain.

CONCLUSION

The results and analysis of this study suggest that there is a significant relationship between blood quinolinic acid levels and the degree of pain in cancer patients with chronic pain. The study found that the greater the level of quinolinic acid, the higher the degree of pain, although this relationship was weak. However, there was no relationship found between quinolinic acid levels and the duration of chronic pain.

In conclusion, this study highlights the potential use of quinolinic acid as a biomarker for assessing pain levels in cancer patients. Further research is recommended, such as a cohort or case control study to compare with cancer patients without chronic pain, in order to obtain more clinically relevant results. Additionally, comparing quinolinic acid levels with kynurenine levels as a biomarker could provide further insight into the relationship between chronic pain and the kynurenine pathway in cancer patients.

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CONFLICT OF INTERESTS

The authors confirm that the content of this article has no conflict of interest.

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