

How to Cite:

Waloejo, C. S., Rehatta, N. M., Andriyanto, L., Sulistiawan, S. S., Pudjirahardjo, W. J., Farhan, A. B., Kurniasari, H., & Chen, Y.-H. (2022). Kynurenic acid as chronic pain biomarker for future cancer pain management. *International Journal of Health Sciences*, 6(S5), 6020–6032.
<https://doi.org/10.53730/ijhs.v6nS5.11277>

Kynurenic acid as chronic pain biomarker for future cancer pain management

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Abstract--The prevalence of chronic pain ranges from 30-50% in patients with cancer undergoing active therapy. Kynurenic acid, xanthurenic acid, and quinolinic acid are significant biomarkers for assessing pain objectively. This study aims to investigate the scientific

evidence of the effect of serum kynurenic acid levels on the severity and duration of chronic cancer pain. It is a cross-sectional study with 80 subjects consisting of 19 male and 61 female patients in the palliative outpatient clinic of Dr Soetomo Hospital. The pain assessment was performed using the NRS, and the biochemical analysis of serum kynurenic acid was assessed using the ELISA method. Of the total of 80 subjects, 26 patients had pelvic organ cancer (33.7%), 24 patients had respiratory organ cancer (30.1%), 17 patients had breast cancer (21.7%), 9 patients had abdominal organ cancer (9.6%), 3 patients had malignant melanoma (3.6%), and 1 patient had sternal bone cancer (1.2%). Kynurenic acid significantly correlated with the severity of pain ($p = 0.043$), with (r) of -0.218 . However, kynurenic acid showed no significant correlation with the duration of pain ($p = 0.052$). Kynurenic acid affected the severity of pain but did not affect the duration of pain in chronic cancer pain patients.

Keywords---Biomarker, cancer, chronic pain, kynurenic acid, pain management, palliative care, pain duration, pain severity

Introduction

Pain is a combination of the physiological, sensory, emotional, and psychological aspects of pain called the subjective aspects (Gelman et al., 2018; Haefeli et al., 2018; ANZCA & FPM; 2020). The pain cascade may be extensive and prolonged but generally resolves within a few weeks. Unsuccessful suppression of this pain response may lead to the development of chronic pain (Meissner et al., 2018). This condition can result in several psychological aspects, including anxiety, changes in behaviour, sleep disorders, and social life disorders. Meanwhile, the resulting physical aspect includes the increase in morbidity and mortality rates (Meissner et al., 2018; Vadivelu et al., 2017). Chronic pain causes limitations in daily activities, dependence on opioids, anxiety, and depression. In addition, the cost of treating patients with chronic pain reaches 560 million to 635 million rupiah per year. The prevalence of chronic pain in the world ranges from 8% to 60% and 30-50% in cancer patients (Gelman et al., 2018; Dahlhamer et al., 2018; Greco et al., 2014). For this reason, chronic pain poses a more significant economic impact than other diseases (Dahlhamer et al., 2018; Philips, 2018).

Pain assessment shall be comprehensively conducted since it leads to various complaints, including impaired physical and psychological function and multiple problems that can worsen the quality of life. Identifying the multidimensional aspects of cancer pain in each individual is the key to developing the most effective therapeutic strategy to increase the quality of life and prevent disorders due to uncontrolled cancer pain (ANZCA & FPM; 2020; Peter et al., 2018; Rodriguez et al., 2019). The high rates of morbidity, dependence on opioids, and failure of conventional treatment indicate the need for more objective measures of chronic pain for more precise management and to improve understanding of the pathophysiology of chronic pain. Several studies have found several biomarkers that are considered to be able to allow more objective chronic pain assessment

than subjective parameters using pain scores (Greco et al., 2017; Amirdelfan et al., 2020; Gunn et al., 2020). Amirdelfan et al. (2020) found that methylmalonic acid, xanthurenic acid, pyroglutamic, kynurenic acid, and hydroxymethylglutarate were significant biomarkers for assessing pain ($p < 0.005$). Meanwhile, Gunn et al. (2020) found that among the assessed biomarkers, quinolinic acid (29%) and kynurenic acid (27%) were the most common abnormal biomarkers of the 17,834 patients they studied. Both were detectable biomarkers of chronic inflammation mediated by proinflammatory cytokines.

Kynurenic acid is a cytokine that has been widely tested for biomarkers of depression. In a recent study, these biomarkers demonstrated the significance of the inflammatory process. The inflammatory reaction is a mechanism for the formation of pain. The kynurenine pathway demonstrates how this cytokine plays a role in the chronic pain process. It is supported by a recent pain study showing that the kynurenine pathway is related to the amino acid tryptophan, which in the process plays a role in producing significant cytokines in the incidence of chronic pain (Amirdelfan et al., 2020; Gunn et al., 2020; Badawy & Donald, et al., 2016). However, there is no available data on the effect of this biomarker on chronic cancer pain. Thus, this study aims to analyze the correlation between kynurenic acid levels and the scales and duration of chronic cancer pain.

Materials and Methods

It is a cross-sectional study of cancer patients with chronic cancer pain who visited the palliative outpatient clinic of Dr Soetomo Hospital from February 2021 until May 2021. The patients were diagnosed with cancer based on the histopathology results, and staging was based on the primary tumour specialist. Patients were enrolled consecutively unless exclusion criteria were applied. The inclusion criteria included an age range of 21 - 65 years, underlying malignancy, and good communication capability (not deaf, not mute, not mentally retarded, and not senile). The exclusion criteria included patients who refused to be the subjects of this study; patients with severe infectious disorders, heart, liver, and kidney failure; patients with haematological disorders, history of using steroid therapy, obesity (BMI > 30), and patients with a history of psychiatric disorders (schizophrenia, psychosis, etc.).

Duration and severity of pain

The duration of pain was analyzed based on cancer patients' medical records. We categorized the patients into two groups: three to six months and more than three months of symptoms. The severity of pain was assessed using the Numerical Rating Scale (NRS). Patients were asked by a third person (nurse of the palliative outpatient clinic) about the numeric level of pain recently. The value ranged from 0 (for no symptom of pain) to 10 (the highest level of pain). A total NRS value of 1-3 was categorized as mild pain, 4-6 was categorized as moderate pain, and 7-10 was categorized as severe pain.

Biochemical analyses

Blood samples were collected from a peripheral vein of cancer patients who visited the palliative outpatient clinic and were stored at -20°C for further analyses. Medical history was collected from medical records, along with blood count and biochemical examination results at the time of collection. According to the manufacturer's instructions, serum kynurenin values were assessed using a kynurenine ELISA kit. Twenty microliters of serum were used from each sample stored at -20°C in the well plate competition. The samples were performed in the laboratory of the Institute of Tropical Disease of Universitas Airlangga.

Ethical considerations

Informed consent for access to medical records and specimens was obtained from each patient. Written informed consent was obtained from participants at the time of serum collection. These processes and study protocols were approved by Komite Etik of Dr Soetomo Hospital (0155/KEPK/III/2021).

Statistical analyses

Multivariate analysis was conducted to determine the relationship of more than one independent variable with one dependent variable. The multivariate analysis was started with a bivariate analysis of each independent variable with the dependent variable. If the results of the bivariate analysis resulted in a p-value of 0.25, the study variables could be included in the multivariate analysis model. The logistic regression test with a p-value of <0.05 indicated a significant value. Data analysis was performed using SPSS ver.26.0 (SPSS, Chicago, IL).

Results

This study involved 80 patients of the palliative outpatient clinic of Dr Soetomo Hospital who met the inclusion and exclusion criteria. The subjects were patients with underlying malignancy, and 26 (32.5%) patients had pelvic organ cancer, 24 patients (30%) had respiratory organ cancer, 17 patients (21.3%) had breast cancer, 9 patients (11.3%) had abdominal organ cancer, 3 patients (3.8%) had malignant melanoma, and 1 patient (1.3%) had sternal cancer.

In this study, the NRS pain scale was utilized, and the results were categorized into mild, moderate, and severe pain. The data revealed that a total of 33 patients had mild pain (39.7%), 40 patients had moderate pain (48.2%), and 10 patients had severe pain (12.1%). Based on the division of chronic pain duration, most patients had symptom duration of 3-6 months (57.8%) and experienced moderate pain (48.2%). The mean kynurenine level in these patients reached 13.31 ug/ml, with the smallest value of 2.89 ug/ml and the highest value of 33.43 ug/ml. Characteristic data can be seen in table 1.

Table 1
Characteristics of subjects

Variables	Mean \pm SD	Median (Min-max)	N (%)	<i>p</i>
Age (year)		54 (21-63)		
Gender				
Male			20 (24.1)	<0.001
Female			63 (75.9)	
Body Mass Index (BMI) kg/m ²	22.80 \pm 3.91			0.161
Comorbid				
None			69 (83.1)	<0.001
Diabetes mellitus			1 (1.2)	
Hypertension			11 (13.3)	
Diabetes mellitus and hypertension			2 (2.4)	
Chronic pain duration				
3-6 months			48 (57.8)	<0.001
> 6 months			35 (42.2)	
Severity of pain				
Mild			33 (39.8)	<0.001
Moderate			40 (48.2)	
Severe			10 (12)	
Kynurenic Acid Level (nmol/L)		13.31 (2.89-33.43)		0.001

* Data normality test: Kolmogorov-Smirnov.

In this study, there was no significant correlation between the duration and scales of chronic pain ($p = 0.364$). Most patients with pain duration of 3-6 months had moderate pain symptoms (54.2%), while most patients with pain duration of > 6 months had mild pain symptoms (48.6%) (Table 2).

Table 2
Pain scales based on the duration of chronic pain.

Chronic Pain Duration	Pain Scales			<i>p</i>
	Mild	Moderate	Severe	
3-6 months	16 (33.3%)	26 (54.2%)	6 (12.5%)	0.364
> 6 months	17 (48.6%)	14 (40%)	4 (11.4%)	

*Kruskal-Wallis test.

In this study, gender, comorbidity, and body mass index did not correlate to kynurenic levels. Based on the Mann-Whitney test, the difference in kynurenic levels in male and female patients resulted in a p -value of 0.624. The kynurenic levels in female patients (13.38 (2.89-33.44) mmol/L) were higher than kynurenic levels in male patients (13.31 (10.58-19.52) mmol/L) (Figure 1).

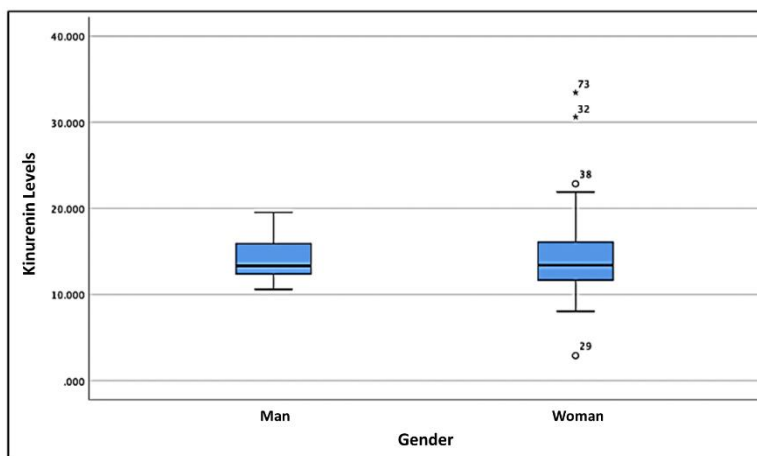


Figure 1. Gender and kynurenic level correlation.

Based on the Kruskal-Wallis test, the difference in kynurenic levels in patients without comorbidity and in those with comorbid hypertension and the combination of hypertension and diabetes mellitus was not significant, with a p-value of 0.926. The kynurenic levels in patients without comorbid (13.35 (9.05-30.61) mmol/L) were higher than those in patients with comorbid hypertension (13.24 (2.89-33.44) mmol/L) or a combination of hypertension and diabetes mellitus (13.12 (12.69-13.55) mmol/L) (Figure 2).

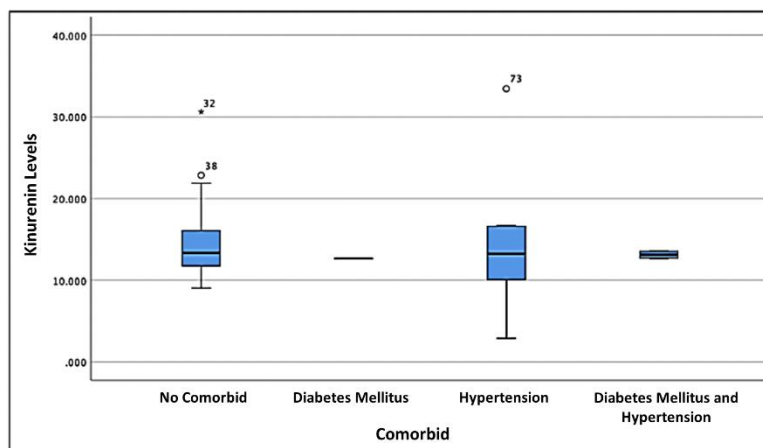


Figure 2. Comorbidity and kynurenic level correlation.

Based on the Kruskal-Wallis test, the difference in kynurenic levels in the BMI classification resulted in a p-value of 0.107. Kynurenic levels in overweight patients (16.16 ± 5.56 mmol/L) were higher than those in patients with normal BMI (13.37 ± 3.39 mmol/L) and in patients with underweight BMI (13.85 ± 2.55 mmol/L) (Figure 3).

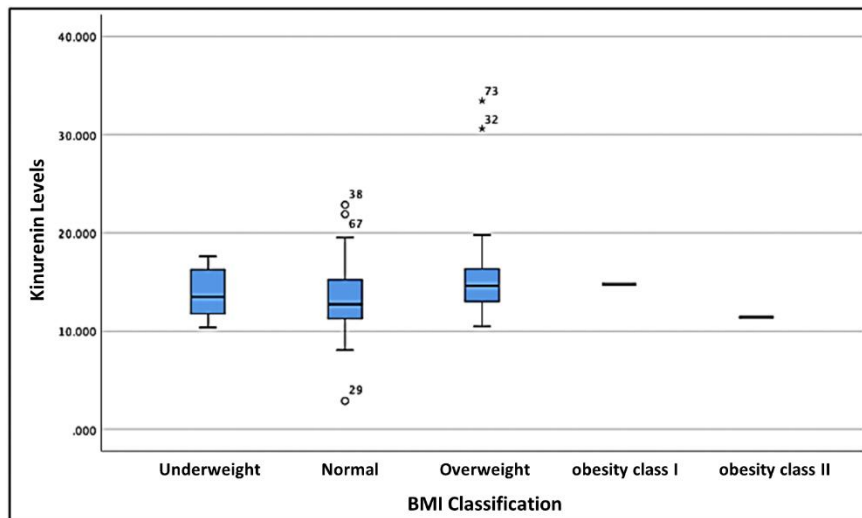


Figure 3. Body mass index and kynurenic level correlation.

Correlation of Kynurenic Acid Levels with Chronic Pain Duration and Pain Scales

The correlation test revealed that there was no significant correlation between the duration of chronic pain and kynurenic acid levels ($p = 0.120$). However, in these results, we found a significant correlation between the pain scales and kynurenic acid levels ($p = 0.048$). Based on the correlation test results, the correlation coefficient (r) was found to reach -0.218 on the kynurenic acid levels and pain scale. It indicated a weak negative correlation between kynurenic acid levels and pain scales. The higher the kynurenic acid levels, the lower the pain scales (Table 3).

Table 3

Correlation of kynurenic acid levels with chronic pain duration and pain scales.

Variables	Kynurenic Acid Levels Median (min-maks) (mmol/L)	p	r
Chronic Pain Duration	12.83 (2.89-33.43)	0.120	0.172
3-6 months	14.07 (10.48-30.61)		
> 6 months			
Chronic Pain Scales		0.048	-0.218
Mild	14.11 (11.13-30.61)		
Intermediate	12.73 (8.05-18.38)		
Severe	12.74 (2.89-33.44)		

*Spearman Test.

Discussion

This study analyzed 80 patients with chronic pain due to malignancy, with the three largest cancer groups being pelvic organ cancer in 26 patients (32.5%),

respiratory organ cancer in 24 patients (30.0%), and breast cancer in 17 patients (21.3%) with a female predominance of 61 patients (76.3%). A total of 66 patients had no comorbid (82.5%), and the most common comorbid was hypertension, found in 11 patients (13.3%). Kynurenic Acid levels in female patients (13.38 (2.89-33.44) mmol/L) were higher than those in male patients (13.31 (10.58-19.52) mmol/L). These results contradict the results of a study by Badawy A and Dougherty and a study by Deac OM et al. Badawy A and Dougherty's study on 114 healthy samples found that kynurenine levels in male patients were higher ($2.17 + 0.18 \mu\text{M}$) than those in female patients ($2.4 + 0.17 \mu\text{M}$), although not significantly different [13,14]. The same results were obtained by Deac OM et al. in their study, stating that in 2,436 healthy samples examined for kynurenic acid levels in the blood, the kynurenic acid levels in male patients were higher (53.9 (29.6-92.5 nmol/L) than those in female patients (40.4 (20.9-74.4) nmol/L), with a significant p-value (Deac et al., 2015).

High levels of kynurenic acid in male patients potentially correlated to tryptophan catabolism. In addition, this study differed from previous studies due to differences in samples. The previous studies took healthy subjects as samples, while this study took patients with malignancy and chronic pain symptoms (Badawy & Donald, 2016; Deac et al., 2015; Kim et al., 2015; Miller et al., 2008). There was no difference between kynurenic acid levels and body mass index (BMI) ($p=0.165$) in this study. Kynurenic acid levels in overweight patients (14.60 (10.48-33.44) mmol/L) had the highest values compared to those in patients with normal BMI (12.73 (2.89-22.85) mmol/L) and in patients with underweight BMI (14.34 (10.35-17.6) mmol/L). This study contradicted a study by Favennec M et al., who found that kynurenic acid levels correlated to body mass index. It was associated with several kynurenine pathway enzyme genes such as indoleamine 2,3-dioxygenase 1 (IDO1), kynureninase (KYNU), kynurenine 3-monooxygenase (KMO), and kynurenine aminotransferase III (CCBL2) increased in omental adipose tissue of obese female patients compared to that of skinny female patients ($p < 0.005$) and their expression was induced by proinflammatory cytokines in primary adipocytes (Sofia et al., 2020; Evrense et al., 2020; Favennec et al., 2015; Prendergast et al., 2017).

This difference might be caused by differences in research subjects. Favennec M et al. in their study, took patients with diabetes mellitus as samples, while this study took patients with chronic pain as samples, with only 3.6% of the study samples suffering from comorbid diabetes mellitus (Miller et al., 2008; Favennec et al., 2015). There was no significant difference in kynurenic acid levels in patients without comorbidity and those with comorbid hypertension and a combination of hypertension and diabetes mellitus ($p = 0.926$). Kynurenic levels in patients without comorbidity (13.35 (9.05-30.61) mmol/L) were higher than those in patients with comorbid hypertension (13.24 (2.89-33.44) mmol/L) or a combination of hypertension and diabetes mellitus (13.12 (12.69-13.55) mmol/L). The study by Pedersen et al. found that kynurenic acid levels in patients with diabetes mellitus were higher (49.4 (37.7-64.5) nmol/L) than those in patients without diabetes mellitus (47.9 (37.1) -61.8) nmol/L). One of the mechanisms that may influence this result is the presence of vascular inflammation in patients with diabetes mellitus, resulting in a blunting of kynurenic acid from tryptophan metabolism. This study contradicted the previous studies because this study took

patients with chronic pain as samples, while Pedersen, in his study, took patients with angina pectoris as samples ((Miller et al., 2008; Prendergast et al., 2017).

Correlation of Kynurenic Acid Levels with Chronic Pain Duration

Based on the division of chronic pain duration, most patients had symptoms of 3-6 months (57.8%). The Spearman correlation test revealed that there was no significant correlation between the duration of chronic pain and kynurenic acid levels ($p = 0.120$). This study is the first that analyzes the correlation between kynurenic acid levels and the duration of pain. Therefore, we cannot provide a comparison with previous studies. In the study by Gunn et al., it was found that the mean blood kynurenic acid level in chronic pain patients reached $1.7 + 0.9$ ug/mg, and the prevalence of abnormal kynurenic acid levels in this study reached 27%. It suggested that kynurenic acid plays a role in the aetiology of chronic pain. The kynurenine pathway will increase the systemic inflammatory response, meaning that increased metabolites can be a sensitive marker of chronic pain systemic inflammation. The mechanism that may influence this result is the upregulation of the kynurenine pathway due to decreased serotonin production, both of which use tryptophan as a substrate (Gunn et al., 2020; Szucs et al., 2020; Sforzini et al., 2019; Savitz 2020).

Decrease serotonin levels not only cause depression but can also decrease the activity of the inhibitory descending pain pathways within normal serotonin levels, resulting in an increase in the pain scale, which can also affect serotonin and nociception levels, and increases susceptibility to neurotoxicity through its interaction with glutamate receptors reseptor (Gunn et al., 2020; Badawy & Donald, 2016; Sforzini et al., 2019; Davis & Liu, 2015). Quinolinic acid is not only a marker of systemic inflammation but also a bioactive modulator of pain perception. Therefore, the activity of the N-methyl-D-aspartate receptor is correlated to the nociceptor system. In the study of Gunn et al., there was a 29% increase in quinolinic acid in patients with chronic pain (Gunn et al., 2020; Sforzini et al., 2019; Savitz, 2020).

Correlation of Kynurenic Acid Levels with Severity of Chronic Pain

In this study, the pain scales were assessed using NRS, and the results were categorized into mild, moderate, and severe pain scales. The data indicated that a total of 33 patients had mild pain (41.3%), 37 patients had moderate pain (46.2%), and 10 patients had severe pain (12.5%). According to the data analysis results, it was found that there was a significant correlation between kynurenic acid levels and the incidence of pain based on pain scales ($p 0.043$). Significant results were also obtained in the study of Gunn et al. in 2020, which was also found to be significant ($p 0.0001$) in a retrospective study. Gunn et al.'s study did not divide pain into categories based on pain scales or duration (Gunn et al., 2020).

In 80 patients who underwent examination and analysis, the correlation coefficient was -0.227 . This value indicated a weak relationship between kynurenic acid levels and pain scales. From the negative r results, we can understand that the higher the patient's pain scale, the lower the kynurenic acid

level. It is in line with the mechanism of formation of kynurenic acid and quinolinic acid in patients with complaints of chronic pain. This value is similar to that obtained in the study of Gunn et al. in 2020, with an r of 0.270 (Gunn et al., 2020; Davis & Liu, 2015; Jovanovic et al., 2020). Kynurenic acid is an endogenous neuroprotectant in the brain in small (nanomolar) concentrations. It is a quinolinic acid antagonist that acts on the NMDA receptor. At low concentrations, kynurenic acid acts as a co-agonist at the glycine modulation site of the NMDA receptor. Meanwhile, at high concentrations, kynurenic acid acts as a competitive inhibitor at the glutamic site of the NMDA receptor and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) (Szucs et al., 2020; Savitz 2020; Davis & Liu, 2015; Jovanovic et al., 2020).

QUIN can selectively activate glutamate N-methyl-D-aspartate (NMDA) receptors, and its accumulation can result in neurotoxicity and disturb glutamatergic transmission (Bender and McCreanor 1985). In the pathway, kynurenic acid (KYNA) is demonstrated to be neuroprotective, counteracting the effects of QUIN. So, there is a balance between neurodegenerative and neuroprotective effects in the kynurenine pathway, expressed by the QUIN/KYNA ratio, which is strictly related to immune activation (Szucs et al., 2020; Sforzini et al., 2019; Vescei et al., 2018; Bostian & Eoff, 2016).

The concentration of quinolinic acid in the brain is normally lower than that in blood and systemic tissues because tryptophan is metabolized more to 5-hydroxytryptamine than to N-formyl kynurenine (NFK). The immune response causes an increase in the activity of the IDO-1 enzyme, which activates the kynurenine pathway so that quinolinic acid levels increase. Inflammatory conditions in the brain cause infiltration of macrophages, microglia, and dendritic cells, which are the largest source of quinolinic acid production. Increased concentrations of quinolinic acid have been found in cerebrospinal fluid in neurodegenerative diseases and animal studies, and it suggests that quinolinic acid is a contributing factor in neurodegenerative diseases associated with inflammation in pain modulation (Prendergast et al., 2017; Davis & Liu, 2015; Jovanovic et al., 2020; Vescei et al., 2018). In this study, there was a significant relationship between kynurenic levels and chronic pain scales. The higher the kynurenic acid level, the lower the patients' pain scales. The coefficient correlation is 0.227, which means the correlation is weak. In this study, there was no relationship between kynurenic levels and the duration of chronic pain.

Acknowledgments

In summary, anxiety, depression, and stress reduced in pregnant women after psychological intervention in the COVID-19 pandemic. Psychocurative reduced anxiety, cortisol, and increased PIBF levels in pregnant women, suggesting that psychological intervention could preserve the mental state during the COVID-19 pandemic. Therefore, it was needed to prevent an adverse outcome of pregnancy. Several efforts are required for further studies, such as the midwife needs to understand the psychological intervention to provide health quality care that consists of physical and mental intervention.

Conflict Of Interest

The named authors have no conflict of interest in conducting this study.

Funding

This study is supported by the Faculty of Medicine, Universitas Airlangga, Surabaya, with a Grant number: 658/UN3.14/PT/2021.

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