

The Relationship between CRP Levels and Depression Severity in Palliative Cancer Patients Experiencing Insomnia at H Adam Malik Central General Hospital Medan

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ABSTRACT

Background: Cancer is a non-communicable disease that is a major health burden worldwide. Sleep disturbances are more commonly reported in cancer patients than in the general population. Sleep disturbances occur in 24-95% of cancer patients. Patients with cancer are more likely to experience depression than the general population. The diagnosis of cancer and the psychological impact have a negative impact on quality of life and the prognosis of the disease. Insomnia can induce systemic inflammation, expression of leukocytes, pro-inflammatory cytokines and necrosis factor, where these inflammatory mediators worsen depression. Its concentration increases in response to inflammation. CRP is an acute-phase reactant induced by IL-6 during the inflammatory or infectious process. Increased CRP levels are associated with inflammation in cancer, depression, and sleep disturbances.

Methods: A cross-sectional study involving hospitalized palliative cancer patients was screened for sleep disturbances using PSQI, screened for depression with BDI, and CRP was examined.

Results: A total of 61 study participants were included in this study. The average PSQI score was 15. Sixty percent of subjects experienced moderate to severe depression. Forty subjects had elevated CRP levels. The results of the

Spearman Rank test showed a positive corelative relationship between CRP levels and depression severity.

Conclusion: There is a significant positive correlation between increased CRP levels and the severity of depression in palliative cancer patients with insomnia.

Keywords: C-Reactive Protein, Depression, Insomnia, Cancer patient

INTRODUCTION

Cancer is a non-communicable disease that constitutes a global health burden, with the number of cases reaching 18.1 million in 2018. Asian countries, such as China, India, and Indonesia, significantly contribute to cancer cases.^{1,2} The prevalence of cancer continues to rise, estimated to reach 21.6 million by 2030, impacting cancer care and healthcare services.³ Indonesia has a cancer incidence rate of 136.2 per 100,000 population, with lung and breast cancers being the most common.^{1,2}

Cancer patients often experience sleep disturbances, with prevalence ranging from 24% to 95%. Sleep disorders can be chronic and affect the well-being and quality of life of patients.^{4,5} Insomnia is often considered a secondary symptom of depression, which can coexist with sleep disturbances. The

combination of sleep disturbances and cancer-related factors can increase the risk of depression, contributing to higher morbidity and mortality.⁶

Depression in cancer patients has a higher prevalence compared to the general population, with an increased risk of suicide. There is a bidirectional relationship between depression, sleep disturbances, and inflammation, with increased levels of C-Reactive Protein (CRP) associated with inflammation in cancer, depression, and sleep disturbances.^{7,8}

A palliative approach for cancer patients helps alleviate suffering and improve the quality of life. Patients receiving palliative care show better emotional health and milder disease symptoms. Palliative care can begin immediately after a cancer diagnosis, alongside cancer treatment, and continue after treatment completion.⁹

MATERIALS & METHODS

This research is an analytical cross-sectional study designed to examine the relationship between C-Reactive Protein (CRP) and the severity of depression in palliative cancer patients experiencing insomnia at RSUP Haji Adam Malik. The research, approved by the ethical commission, will be conducted from August to November 2023 at RSUP H. Adam Malik Medan. The sample includes all cancer patients at the hospital from the issuance of ethical clearance until the sample size is met in November, with a minimum of 51 samples determined using a formula and selected through consecutive sampling.

Inclusion criteria involve cooperative patients willing to provide informed consent, aged over 18, meeting Ministry of Health criteria for palliative care, and experiencing insomnia (PSQI score > 5). Exclusion criteria include patients with decreased consciousness, those passing away before CRP examination, and those refusing CRP examination.

The examination process encompasses obtaining consent, conducting anamnesis for demographic data, assessing sleep quality using PSQI, diagnosing depression with BD-II, and measuring CRP levels through venous blood samples and immunoassays. The study aims to shed light on the relationship between CRP, depression severity, and insomnia in palliative cancer patients.

STATISTICAL ANALYSIS

The data analysis in this study involves presenting basic characteristic data descriptively, testing for normality using the Kolmogorov-Smirnov test, and examining the correlation between CRP and the severity of depression with Spearman's test. A p-value <0.05 will be considered statistically significant.

RESULT

This study involves 61 palliative cancer subjects experiencing inpatient insomnia at RSUP H. Adam Malik. The demographic characteristics of the research subjects are provided in Table 1. Prevalence scores of each variable and its median are as presented in Table 2.

Table 1: Sample demographic characteristics

Demographic Characteristics	N=61 (%)
Age (years, median)	52
Gender	
- Female	31 (50.8%)
- Male	30 (49.2%)
Marital status	
- Not married	8 (13.1%)
- Married	53 (86.9%)
Cancer type	
- Cervical cancer	10 (16.4%)
- Hepatocellular carcinoma	7 (11.5%)
- Breast cancer	
- Lymphoma	6 (9.8%)
- Ovarian cancer	5 (8.2%)

- Others	5 (8.2%) 33 (45.9%)
Duration length since diagnosed of cancer (months, median)	6 months
Duration of sleep (hours, median)	4 hours

Table 2: Variable prevalence scores of palliative cancer patients experiencing insomnia

Variable	N (%)
PSQI (median, range)	15, 6-21
CRP	
Median (mg/dL, median)	0.7
Normal	21 (34.4%)
Elevated	40 (65.6%)
BDI	
BDI (score, median)	24
Mild depression	17 (27.9%)
Moderate depression	20 (32.8%)
Severe depression	24 (39.3%)

To determine the relationship between CRP levels and the severity of depression, the Spearman test was conducted. The results of the Spearman test indicate a statistically significant relationship between CRP levels and the severity of depression ($p < .001$), as presented on Table 3.

Table 3: Spearman test to analyse for relationship between CRP levels and depression severity

BDI (depression)	CRP (median, mg/dL)		Total	Asymptomatic Significance
	Normal	Elevated		
Mild	15	2 (0.7)	17	<.001
Moderate	5	15 (1.08)	20	
Severe	1	23 (1.1)	24	
Total	21	40	61	

DISCUSSION

This study assesses the elevation of CRP concerning depression and sleep disorders in palliative cancer patients at RSUP Haji Adam Malik. The majority of subjects are married (86.9%), with 31 females (50.8%) and a median age of 52. The prevalent cancer types include cervical (16.4%), hepatocellular carcinoma (11.5%), breast cancer (9.8%), lymphoma (8.2%), and ovarian cancer (8.2%). Previous studies by Naser et al. (2021) and Xu et al. (2021) on cancer patients reveal demographic details and common cancer types. Sleep disorders in cancer patients are attributed to various factors, such as stress, mental disorders (like depression and anxiety), pain, and treatment side effects.^{10,11}

Poor sleep quality and sleep disturbances significantly impact cancer and can serve as predictors. These disturbances affect

psychological and physiological mechanisms, contributing to fatigue related to cancer. The role of daytime sleep in fatigued cancer patients remains unclear, and it may not necessarily alleviate fatigue. Numerous causes contribute to sleep disturbances in cancer patients, ranging from organic factors like pain and treatment to psychosocial pressures such as anxiety, depression, and concerns about family or financial situations.¹²

Depression and mood changes are common reactions to cancer, often manifesting in sleep disturbances. The study by Strik et al. (2021) finds a significant relationship between depression and sleep disturbances in palliative cancer patients, with nearly half experiencing mild or moderate mood depression.¹³⁻¹⁵ In this study, over 60% of palliative cancer patients experience mild to severe depression, measured by the Beck Depression Inventory (BDI).

Cancer disrupts the central circadian regulation, increasing the risk of sleep disturbances. Treatment-related toxicities, including tissue damage, bone marrow suppression, fatigue, anxiety, pain, and depression, are associated with an elevated risk or exacerbation of existing sleep disorders. Increased pro-inflammatory cytokine regulation can persist after treatment cycles, affecting REM sleep loss. Patients experiencing toxic side effects from cancer treatment often have further reductions in sleep quality, impacting treatment resistance, disease progression, quality of life, and survival.^{6,16}

The study reveals that 65.6% of subjects experience elevated CRP levels, indicating variations related to cancer stage, progression, and complications. CRP is considered a predictor of prognosis, treatment outcomes, and tumour recurrence. Proinflammatory cytokines contribute to depressive symptoms in cancer patients, with elevated CRP levels predicting

depression development and resistance to antidepressant therapy.¹⁷

A meta-analysis by Howren et al. (2009) establishes a connection between clinical depression and inflammatory markers like C-reactive protein (CRP), IL-6, IL-1, and IL-1.^{8,18} In this study, the association between depression severity and increased CRP levels is significant ($p < 0.001$), indicating a meaningful difference in CRP values.

In a study by Kwekkeboom et al. (2018) assessing the role of inflammation in pain, weakness, and sleep disturbances in cancer patients, psychological stress positively correlates with a cluster of symptoms. CRP ($\beta = 0.24$, $p = 0.011$) and IL-1 β ($\beta = 0.24$, $p = 0.011$) with high values have associations with pain, weakness, and sleep disturbances in cancer patients.¹⁹

CONCLUSION

The study found that palliative cancer patients with insomnia in this research had an average PSQI score of 15, and about two-thirds of them experienced moderate to severe depression. Patients with insomnia also tended to have elevated CRP levels. Additionally, there is a significant positive correlation between increased CRP levels and the severity of depression in these patients. Recommendations for future research include using larger samples for more accurate and generalizable results, consider CRP levels as a parameter for predicting depression and implementing faster psychosocial interventions, and further exploring of mechanisms and interventions for preventing and treating depression in palliative cancer patients with insomnia.

Declaration by Authors

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