International Journal of Research and Review
Vol. 10; Issue: 4; April 2023
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

High C-Reactive Protein (CRP) Levels as Risk Factors for Poor Sleep Quality in Patients with Nasopharyngeal Cancer with Radiotherapy

I Gst Ayu Agung Aria Tristayanthi[1], Desak Ketut Indrasari Utami[1], I Made Oka Adnyana[1], Anak Agung Ayu Putri Laksmidewi[1], Anna Marita Gelgel[1], I Komang Arimbawa[1]

[1]Deparment of Neurology, Udayana University/Prof. Dr. IGNG Ngoerah Hospital, Denpasar, Bali, Indonesia

Corresponding Author: Desak Ketut Indrasari Utami

DOI: https://doi.org/10.52403/ijrr.20230454

ABSTRACT

Background/aim: Good sleep quality affects the body's metabolism, which impacts a person's physical and psychological condition. Patients with nasopharyngeal cancer who receive radiotherapy are reported to experience a lot of poor sleep quality, which will affect the success of treatment, increase treatment costs and decrease quality of life, which will cause social problems in the community future. Rate C-Reactive Protein (CRP) serum in nasopharyngeal cancer patients with radiotherapy increased significantly after radiotherapy. This study to Proving rate of CRP is a risk factor for poor sleep quality in nasopharyngeal cancer patients with radiotherapy

Method: This is a statistical analytical study with a case-control design in nasopharyngeal cancer patients with radiotherapy at Prof. Dr. IGNG Ngoerah Hospital Denpasar, Bali, from December 2020 to April 2021. Data analysis using SPSS for Windows.

Results: There were 120 respondents, 77.5% male, mean age ± SD 52.85 ± 6.35, high CRP levels on average with poor sleep quality 16.95 ± 6.95 mg/L. Bivariate analysis using Chi-square obtained OR = 9.33 (95% CI 2.18-39.9; p = 0.003). The results of multivariate analysis showed that the CRP level variable had p=0.003. There is a significant relationship between high CRP levels and poor sleep quality.

Conclusion: High CRP levels increase the risk of poor sleep quality nine times in nasopharyngeal cancer patients with radiotherapy

Keywords: poor sleep quality, CRP, nasopharyngeal cancer, radiotherapy

INTRODUCTION

Cancer is an abnormal growth of body cells that is uncontrolled. These cancer cells will enter the body's normal tissues. Normal cells are damaged and die, and cancer cells divide and grow uncontrollably. Cancer cells enter the blood system after leaving the stem cells and lymph nodes to other cell organs, where the runaway growth cycle occurs again, called a metastatic process.[1]

Nasopharyngeal cancer (NPC) arises in the nasopharynx (above the throat and behind the nose), as evidenced by a mild microscopic squamous differentiation process or ultrastructure.[2] Risk factors for nasopharyngeal cancer include heredity and genetics, dietary factors, hormones, lifestyle, smoking, alcohol consumption, obesity, chronic infection, age, and stress.[2,3]

Epidemiology of cancer According to Canadian Center Statistics, in 2019, there were 220,440 new cases. The most common types of cancer were lung cancer (27,200 cases), breast cancer (26,300 cases), colorectal cancer (26,300 points), and prostate cancer (22,900 cases). The

incidence of cancer in Canada is not too significant; there is a substantial difference between the sexes of men: and women, namely 113,000: 107,400 new cases. Women are more likely to develop cancer in the age range of 25-59 years. The average incidence of cancer occurs at the age of >60 years.[4] Data in Indonesia (2019) Nasopharyngeal Cancer (NPC) is a malignancy that ranks 4th after breast, cervical, and lung cancer. Based on GLOBOCAN in 2012 stated that 87,000 new cases of NPC are detected every year (with a ratio of 61,000 in men and 26,000 in women). The death rate from NPC reaches 36,000 in men and 15,000 in women. NPC is more common in men than women, namely 2.18: 1 with 60% with a mean age of 25-60 years. The highest incidence of NPC worldwide is found in Southeast China, with 40-50 cases of NPC out of 100,000 population.[5,6]

NPC is rarely found in Europe and North America, with a very low incidence of less than 1/100,000 population.[3,7] The number of visits to the Radiotherapy Installation at Prof. Dr. IGNG Ngoerah Hospital Denpasar is occupied mainly by breast, cervical, nasopharyngeal, and prostate and colon cancer. The incidence of NPC at Prof. Dr. IGNG Ngoerah Hospital in 2014-2016, where the highest number found in 2016 was 114 cases. Based on age found, swimming aged 36-65 years with a male-dominated gender, namely 75 people (65.79%). The most common stadium is located in Prof.Dr. IGNG Ngoerah Hospital is stage IVA 46 people (40.35%) out of 69.[8]

Treatment for nasopharyngeal cancer includes radiotherapy, chemotherapy, surgery, and immunotherapy. Treatment is selected according to the size of the cancer and will differ for each individual. Treatment can be with one type or a combination of several treatments (National Cancer Institute (NCI),2020).[9] Radiation technology was carried out from 1927 until 2013. Radiotherapy service centers have around 29 locations spread throughout Indonesia. Radiotherapy is the gold standard for therapy in nasopharyngeal cancer (NPC). The Government of Indonesia issued the Minister of Health Regulation Number 1427 of 2006 concerning Standards for Radiotherapy Services in Hospitals and Minister of Health Regulation Number 81 of 2013 concerning the administration of radiographers. Of the 10.9 million people diagnosed with cancer worldwide each year, about 50% require radiotherapy. The cost of radiotherapy is calculated to save 5% of the total cost of cancer treatment. Radiotherapy is used as curative, comforting, and preventive therapy. Curative therapy is a single therapy often used in cases of Hodgkin's Lymphoma and glottic cancer in the early stages. Palliative therapy is preferred in brain cancer, bone cancer and superior vena cava syndrome cases. Preventive therapy here is to prevent the occurrence of a process of spread (metastasis) to other organs in cases of acute lymphoblastic leukemia with whole-brain radiotherapy and small-cell lung cancer. Radiation therapy can achieve the therapeutic effect by inducing apoptosis, autophagocytosis, cell necrosis, and mitotic death. Some of the reported side effects of radiotherapy include skin toxicity, pain, sleep disturbances, xerostomia and hyposalivation, and cardiac abnormalities.[10]

Rate C-Reactive Protein (CRP) serum in nasopharyngeal cancer patients with radiotherapy reported a significant increase after receiving radiotherapy within four weeks. Serum CRP levels decreased at four weeks after discontinuation of radiotherapy. This increase in serum CRP is associated with acute mucositis, decreased immune status, pain, fatigue, toxicity and sleep quality.[11] A United Kingdom study with 6465 samples found that poor sleep quality was associated with increased CRP.[12]

Sleep is integral to every individual's daily routine; survival is equated with eating and drinking. Good sleep is associated with physical, cognitive and psychological well-being.[13] Sleep is one of the functions of

life, and the process that occurs during sleep is still being studied. It is known that various medical disorders can affect the quality of human life and even interfere with health which can be life-threatening. During sleep, there are fluctuating and dynamic changes in the cardiovascular, respiratory and metabolic nervous systems.[14] Sleep is defined as a physiological condition in which there is a decrease in consciousness and a decline in global cognitive function in the brain that is reversible and repetitive. Sleep conditions can be awakened by providing sensory stimulation or other stimuli. Sleep disturbances can affect the biological processes of cancer cells, recovery, quality of life, morbidity and mortality. Symptoms of each cancer, cancer treatment, and psychological stressors influence sleep disorders, affecting the decline in function and quality of life.[15] Research on sleep quality disorders found about 44% (36 cases out of 81 patients met) who experienced sleep quality disorders in radiotherapy patients at Prof. Dr. IGNG Ngoerah Hospital Denpasar. The mean age of those who experience sleep quality disorders is 50 years, where the male: female ratio is 1.2:1. It was found that there was poor sleep quality with sleep latency disorders with a mean PSQI value of 8.69.[16]

Sleep disorders and inflammation have yet to be studied more deeply. The mechanisms involved between sleep disturbances and inflammation are the hypothalamus-pituitary-adrenal (HPA) axis and the Sympathetic nervous system (SNS), which enhances the proinflammatory profile. Activation of-adrenergic stimulates improvement of activity of Nuclear Factor kappa Beta (NF-kB), expression of inflammatory genes, production of proinflammatory cytokines and markers of systemic inflammation. Normal nocturnal sleep cycles decrease sympathetic activation. The presence of activation of the sympathetic pathway is a biological factor that explains the occurrence of sleep disturbances, short sleep duration and increased inflammatory markers.[17] A study conducted by Irwin et al. in 2015 that assessed inflammatory markers Interleukin6 (IL-6) and CRP found an increase in both inflammatory markers found in the population with sleep disorders, where the increase in CRP was higher and more in the population with more severe sleep disorders. Decreased sleep duration was also found with increased CRP and IL-6.[12,17,18]

Radiotherapy stimulates proinflammatory, profibrotic, proangiogenesis and cytokine changes in tumour tissue. CRP, as a marker of inflammation, is associated with the outcome of sleep disturbances and fatigue in head and neck tumour patients receiving radiotherapy.[19] High CRP levels have high accessibility, are easy to carry out in various scientific studies, and are more affordable than other inflammatory marker indicators, so they are more applicable in daily clinical practice. Therefore, more research is needed to determine whether increased CRP is a risk factor for sleep disturbances in radiotherapy patients. The number of studies that are still small on CRP levels High CRP levels as a risk factor for poor sleep quality in radiotherapy patients are the reason for researchers to study high CRP levels as a risk factor for poor sleep quality in patients with radiotherapy.

METHOD

This analytical observational study uses a case and control study design to determine high serum CRP levels (> 10 mg/dl) as a risk factor for sleep quality in nasopharyngeal cancer patients with radiotherapy. The research was conducted at the Radiotherapy Installation of Prof. Dr. IGNG Ngoerah Hospital Denpasar from December to April 2021. The ethical license for this study was No. 2405/U.N. 14.2.2VII.14/L.T./2020 from the research ethics committee of the Faculty of Medicine, Udayana University/ Prof. Dr. IGNG Ngoerah Central General Hospital Denpasar.

Case inclusion criteria in this study were: (1) Stage III-IV nasopharyngeal cancer patients who received radiotherapy with a minimum dose per fraction of 2 Gy up to a total dose of 67.5 Gy for at least four weeks who experienced sleep disturbances, (2) Cancer patients aged 40 – 60 years old, (3) signed informed consent.

Exclusion criteria in the case and control groups in this study were: (1) Stage III-IV nasopharyngeal cancer patients who received radiotherapy with a minimum dose per fraction of 2 Gy up to a total dose of 67.5 Gy for at least four weeks who did not experience sleep disturbances, (2) Cancer patients aged 40-60 years (3) Nasopharyngeal cancer patients with radiotherapy with significant depression, severe anxiety disorders, use of drugs that affect sleep such as antipsychotics, antidepressants, anti-anxiety as in the last 30 days recorded in the medical record, (4) Nasopharyngeal cancer patients who are being exposed to local infections or systemic infections recorded in the medical record, (5). Patients experiencing trauma include head trauma and bone trauma recorded in the medical record, (6) Patients on anti-inflammatory therapy include dexamethasone, prednisone, prednisolone, methylprednisolone recorded in the medical record, (7) Patients with complaints of head and neck pain, neuropathic pain. The results of the study will be analyzed statistically with the help of the program Windows SPSS version 23 in statistical stages descriptive, bivariate analysis Odds Ratio (OR), and multivariate analysis. The significance level is $p < 0.05$ with a 95% confidence interval.

RESULT

The study involved 120 respondents of nasopharyngeal cancer patients with radiotherapy at Prof. Dr. IGNG Ngoerah Hospital Denpasar who met the eligibility criteria, grouped into a case group with poor sleep quality (60 respondents) and a control group with good sleep quality (60 respondents). The characteristics of the research respondents are in **Table 1.**

Table 1 Basic characteristics of Respondent

Demographic Profile		**Cases (60 Subjects) n(%)**	**Control (60) Subject) n(%)**
Gender	Man	45 (75)	48 (80)
	Woman	15 (25)	12 (20)
Age	40-50 years	21 (35)	15 (25)
	51-60 years old	39 (65)	45 (75)
Mean Age ± S.D. (years)		51.65 ±6.72	54.05 ± 5.88
Patient stage	III	12 (20)	24 (40)
	IV	48 (80)	36 (60)
Radiotherapy	Series 1	45 (75)	48 (80)
	Series > 1	15 (25)	12 (20)
Depression	Normal	33 (55)	45 (75)
	Mild to moderate	27 (45)	15 (25)
Anxiety	Normal	33 (55)	42 (70)
	Mild to moderate	27 (45)	18 (30)
Serum CRP level	High	42 (70)	12 (20)
	Normal	18 (30)	48 (80)
Average CRP level ±SD (mg/L)		16.95±6.95	7.55±4.87

In this study, a bivariate analysis was conducted to aim for high CRP levels as a risk factor for poor sleep quality in nasopharyngeal cancer patients with radiotherapy (**Table 2**).

Table 2 Bivariate Analysis

Variable		**Case N (%)**	**Control n (%)**	**OR**	**IK 95%**	**P***
Gender	Man	45 (75)	48 (80)	1.58	0.24-1.70	0.635
	Female	15 (25)	12 (20)			
Age (years)	40-50	21 (35)	15 (25)	0.62	0.16-2.43	0.492
	51-60	39 (65)	45 (75)			
Radiotherapy	Series 1	12 (20)	24 (40)	1.33	(0.30-5.93)	0.705
	Series > 1	48 (80)	36 (60)			
Cancer stage	III	45 (75)	48 (80)	2.67	0.65-10.97	0.174
	IV	15 (25)	12 (20)			

Table 2 To Be Continued…						
Depression	Normal	33 (55)	45 (75)	2.45	0.64-9.40	0.190
	Mild to moderate	27 (45)	15 (25)			
Anxiety	Normal	11 (55)	42 (70)	1.91	0.52-7.01	0.330
	Mild to moderate	9 (45)	18 (30)			
Serum CRP level	High	42 (70)	12 (20)	9.33	2.18-39.9	0.003†
	Normal	18 (30)	48 (80)			

*** Chi-Square test**
†Significant

This study also carried out a multivariate analysis with the aim of high CRP levels as a risk factor for poor sleep quality in nasopharyngeal cancer patients with radiotherapy (**Table 3**).

Table 3 Multivariate Analysis of Logistic Regression

Characteristics	Adjusted OR	95% CI	P*
Step 1			
Depression	0.620	0.306-16,071	0.431
Cancer Stage	0.593	0.888-2.881	0.441
CRP	7,050	0.12-0.513	0.008
Step 2			
Depression	0.371	0.273-11.783	0.542
CRP	7,289	0.12-0.494	0.007
Step 3			
CRP	9.33	0.25-0.459	0.003†

***Logistic regression test**
†Significant

DISCUSSION

This study found that the sexes of 93 (77.5%) male respondents and 27 female (22.5%). Wicaksono (2019) population of cancer nasopharynx is dominated by men 50 (72.5%) and women 19 (27.5%). The research results obtained by Marlinda (2014) regarding the incidence of nasopharyngeal cancer in Indonesia in 2014 was 9,355 cases, with male dominance three times greater than women at 70.4%.[20] Poor sleep quality disorders in male nasopharyngeal cancer patients were found to have an increase in p = 0.008.[21]

The mean age of respondents was higher in the control group, namely 54.05 years with a standard deviation of 5.880, compared to the case group of 51.65 years with a standard deviation of 6.722. This research was carried out by matching age at the beginning of the study. However, due to data limitations, the age difference of fewer than 3 years is still included in this study, so there is a difference in the mean age in the two groups with a similar range. The results were obtained by Wicaksono (2019), where the age range of nasopharyngeal cancer patients at Prof. Dr. IGNG Ngoerah Hospital Denpasar is 46-65 years, and Kiprian (2018) is 40-69 years.[22] According to Lai (2018), age 42.6±10.2 affects poor sleep quality with QR 1.06 (95% CI 1.01–1.10; p=0.008).[21]

The most NPC stadiums that underwent radiotherapy were NPC patients with stage IV (80%). This is to a study conducted by Wicaksono (2019) on the characteristics of nasopharyngeal cancer patients at the ENT-KL polyclinic, Prof. Dr. IGNG Ngoerah Hospital Denpasar in 2015 as many as 34 (49.3 %) stage IVA and 17 (24.6%) stage IVB.[22] Kiprian et al. (2018) found that there were disturbances in sleep quality in patients with head and neck cancer in stages IVA and III.[11] Lai et al. (2018) said there were disturbances in the quality of sleep of nasopharyngeal cancer patients at stage IV, which was 60.4%, while 25.7% were found in stage III.[21]

The first series of radiotherapy covers several cycles. The duration of radiotherapy in the first series was found to be more, namely 45 (75%) in cases and 48 (80%) in controls. Sleep quality disturbances were found to occur in the first series of radiotherapy 33 (64.7%) with p=0.003.[23] Mo et al. (2020) had impaired sleep quality after the first radiotherapy series with p<0.001. Mild to moderate depression was 27 (45%), and mild to moderate anxiety was 27 (45%). In the study, 33 people (55%) did not experience stress, and 33 people 70%) did not experience depression. Mo et al. (2014) found 31 (60.1%) NPC patients after radiotherapy did not experience depression, and 20 (39.2%) experienced depression.[23] The level of anxiety in patients with nasopharyngeal cancer at Prof. Dr. IGNG Ngoerah Hospital in 2016 obtained 8

respondents (17%) with mild anxiety and 12 subjects (25.5%) with severe anxiety.[24]

The incidence of NPC is ranked fourth in Indonesia. Radiotherapy is the gold standard therapy for NPC at all stages. Giving radiotherapy as early as possible will result in a higher survival rate. But every treatment has an unavoidable effect. Radiotherapy has an impact not only on the location of radiation but on various changes throughout the body. The incidence of sleep quality disorders was 57% with PSQI in patients after radiotherapy.[10]

CRP production is affected by proinflammatory cytokines, such as IL-6, IL-1, and TNF-α. Monocytes or macrophages secrete proinflammatory cytokines after receiving inflammatory stimulation. The pro-inflammatory cytokine that produces the most CRP secretion is IL-6. This is said in a study that found a positive relationship between Il-6 concentration and serum CRP levels. Multivariate analysis in this study obtained an OR of 3.04 (95% CI, p=0.017).[18]

Systemic inflammation is indicated by an increase in IL-6 and CRP associated with side effects of radiotherapy in head and neck cancer.[11] Many proinflammatory cytokines play a role in Non-REM sleep. An increase in proinflammatory cytokines will stimulate CRP secretion in both acute and chronic phases, which will cause a decrease in sleep duration.[25] The increase in serum CRP after radiotherapy will cause interactions on the HPA axis, stimulating the formation of cortisol and increased glucocorticoids. This will increase the decrease in sleep duration. The mechanism between high levels of CRP and poor sleep quality is shown in **Figure 1**. This study found 42 (70%) respondents with elevated CRP levels in the case group and 12 respondents (20%) in the control group. Bivariate analysis with Chi-square done so that OR = 9.33 (I.K. 95% = 2.18-39.96; p = 0.003), which means that high CRP levels as a risk factor for poor sleep quality in nasopharyngeal cancer patients with radiotherapy increase the risk 9.33 times to experience poor sleep quality compared to normal CRP levels. Sylvie et al. (2017) found an association between higher CRP levels with sleep problems ($p < 0.001$) which are in line with this study.[26] Katano (2017) on the increase in CRP in hypopharyngeal cancer patients after radiotherapy, which causes sleep quality disturbances with $p<0.001$.[18] Research conducted by Kiprian (2018) regarding radiotherapy that stimulates an increase in CRP in head and neck patients is associated with poor sleep quality with P = 0.004 according to this study.[11]

Other factors considered to influence the risk of poor sleep quality in nasopharyngeal cancer patients with radiotherapy are gender, age, stage of cancer, duration of radiotherapy, depression, and anxiety. The bivariate analysis results did not show a significant relationship between other variables and the risk of poor sleep quality in nasopharyngeal cancer patients with radiotherapy. The age variable differed from Lai's (2018) study, namely 42.6±10.2, which affected poor sleep quality with an OR of 1.06 (95% CI 1.01–1.10; p=0.008).[21] The age difference is due to this study's limited number of samples.

Variables of mild-moderate depression and mild-moderate anxiety were limited in this study by research conducted by Lai (2018), Lee (2018) and Pössel (2019) that major depression and severe anxiety can affect sleep quality.[21,27,28]

This study performed a multivariate logistic regression analysis to assess independent risk factors for poor sleep quality. The results of multivariate analysis showed that the independent factor influencing poor sleep quality in nasopharyngeal cancer patients with radiotherapy was CRP OR 9.061 (95% CI = 0.25-0.459; p = 0.003).

This study's results align with Liu (2014), who found a relationship between poor sleep quality and increased CRP in China. Poor sleep quality is the result of disruption of the HPA axis.[12] Another study by Kiprian (2018) found that poor sleep quality was significantly associated with increased

CRP levels.[11] Association between the increased elevation of the inflammatory marker CRP and impaired sleep quality in American adults.[29]

The strong relationship shown between serum CRP levels and poor sleep quality in nasopharyngeal cancer patients with radiotherapy can be the basis for further studies on this topic so that a more clear causal relationship between increased serum CRP levels and the incidence of sleep quality can be seen in nasopharyngeal cancer patients with radiotherapy.

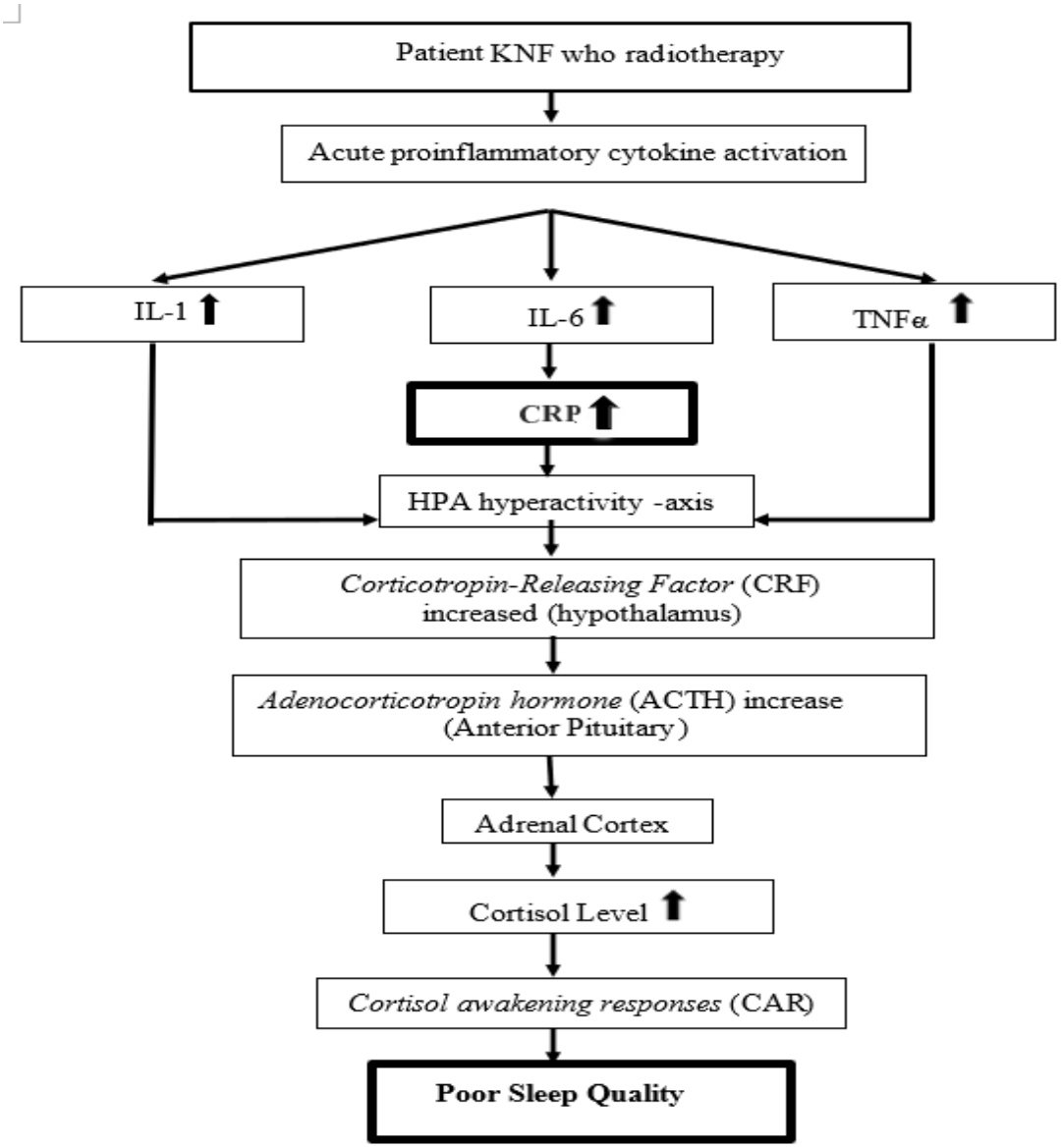

Figure 1 Mechanism of increased CRP with poor sleep quality

The advantage of this study is that not many researchers have investigated the levels of CRP as a risk factor for poor sleep quality in nasopharyngeal cancer patients with radiotherapy, especially in Indonesia and Bali, in particular. The research respondents used were homogeneous, which was carried out by matching age and sex in cases and controls. Respondents in the research explained the procedure for filling out the questionnaire; research respondents filled out the questionnaire themselves without the researcher's influence, which was more accurate. The study uses an instrument tested for reliability and validity in Indonesia with good results.

The weakness of this study is that it cannot determine the minimal increase in CRP

levels that causes poor sleep quality. This study uses respondents from specific populations and is carried out in certain places, so the results cannot describe the same conditions in different people and places.

CONCLUSION

Based on the results of this study, it was concluded that high CRP levels increased 9.3 times the risk of poor sleep quality, which was statistically significant in nasopharyngeal cancer patients with radiotherapy.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Fan AM. Cancer. Inf Resour Toxicol. 2009;103–21.
2. Komite Penanggulangan Kanker Nasional Kemenkes RI. Panduan Penatalaksanaan Kanker Nasofaring. Kementeri Kesehat Republik Indones Kom Penanggulangan Kanker Nasional. 2015;1–56.
3. Wijaya FO, Soeseno B. Deteksi Dini Dan Diagnosis Karsinoma Nasofaring. Cdk-254. 2017;44(7):478–81.
4. Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, et al. Projected estimates of cancer in Canada in 2020. Cmaj. 2020;192(9):E199–205.
5. Wei K-R, Zheng R-S, Zhang S-W, Liang Z-H, Li Z-M, Chen W-Q. Nasopharyngeal carcinoma incidence and mortality in China, 2013. Chin J Cancer. 2017;36(1):1–8.
6. Gondhowiardjo SA, Silalahi M, Manuain DA, Sekarutami SM, Christina N, Octavianus S, et al. Cancer Profile in Central Jakarta : A 5-Year descriptive study. Radioter Onkol Indones. 2018;9(2):34–42.
7. Sigarlaki ED, Imanto M, Cania E. Tatalaksana Radioterapi pada Karsinoma Nasofaring. Pengobatan Radioter pada Karsinoma Nasofaring Tatalaksana. 2019;8(2):23–6.
8. Maubere F, Nuaba IGA. Poliklinik Telinga Hidung Tenggorokkan-Kepala Leher Rumah Sakit Umum Pusat Prof. Dr. IGNG Ngoerah Denpasar Pada Bulan November-Desember 2014. Ojs Unud. 2014;1–18.
9. Neoh May Kay, Zalina Abu Zaid, Zuwariah Abdul Rahman N, Jamhuri, Zuliehaiza Kahairudin, Siti Noraini Ahmad Samwil A, Abdullah, Ho Chiou Yi, Betti Sharina Haniff Lai, Ng Wai Han AM, Mohammad, Nor Baizura Md Yusop ZI& Z 'Azuan M, Daud. Factors associated with malnutrition among head and neck cancer in-patients before radiotherapy in National Cancer Institute,. 2020;26(2):257–71.
10. Fitriatuzzakiyyah N, Sinuraya RK, Puspitasari IM. Cancer Therapy with Radiation: The Basic Concept of Radiotherapy and Its Development in Indonesia. Indones J Clin Pharm. 2017;6(4):311–20.
11. Kiprian D, Czarkowska-Paczek B, Wyczalkowska-Tomasik A, Fuksiewicz M, Kotowicz B, Paczek L. Radiotherapy and radiochemotherapy increase serum levels of proinflammatory interleukin-6 and C-reactive protein in patients with head and neck cancers. Transl Cancer Res. 2018;7(1):41–7.
12. Liu R, Liu X, Zee PC, Hou L, Zheng Z, Wei Y, et al. Association between sleep quality and C-reactive protein: Results from national health and nutrition examination survey, 2005-2008. PLoS One. 2014;9(3):2005–8.
13. Crivello A, Barsocchi P, Girolami M, Palumbo F. The Meaning of Sleep Quality: A Survey of Available Technologies. IEEE Access. 2019;7:167374–90.
14. Islamiyah WR. Panduan Tatalaksana Gangguan Tidur. PERDOSSI. 2018;2:466.
15. Redeker NS, Pigeon WR, Boudreau EA. Incorporating measures of sleep quality into cancer studies. Support Care Cancer. 2015;23(4):1145–55.
16. Lestari YI, Utami DKI, Budiarsa IGN, Widyadharma IPE. Korelasi Kualitas Tidur dengan Fungsi Kognitif pada Lansia di Desa Tonja, Denpasar. Neurona. 2017;34(December):201–2.
17. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: A systematic review and

meta-analysis of cohort studies and experimental sleep deprivation. Biol Psychiatry. 2016;80(1):40–52. DOI: 10.1016/j.biopsych.2015.05.014
18. Katano A, Takahashi W, Yamashita H, Yamamoto K, Ando M, Yoshida M, et al. The impact of elevated C-reactive protein level on the prognosis for oro-hypopharynx cancer patients treated with radiotherapy. Sci Rep. 2017;7(1):1–2. DOI: 10.1038/s41598-017-18233-w
19. Hu JJ, Urbanic JJ, Doug Case L, Takita C, Wright JL, Brown DR, et al. Association between inflammatory biomarker C-reactive protein and radiotherapy-induced early adverse skin reactions in a multiracial/ethnic breast cancer population. J Clin Oncol. 2018;36(24):2473–82.
20. Adham M, Rohdiana D, Mayangsari ID, Musa Z. Delayed diagnosis of nasopharyngeal carcinoma in a patient with early signs of unilateral ear disorder. Med J Indones. 2014;23(1):52–7.
21. Lai XY, Tang ZM, Zhu XD, Li L, Qin XY, Lan JL, et al. Sleep Disturbance and Related Factors in Patients with Nasopharyngeal Carcinoma and Their Family Caregivers Prior to the Initiation of Treatment. Sci Rep. 2018;8(1):1–8. DOI: 10.1038/s41598-018-32587-9
22. Wicaksono GOS. Karakteristik pasien kanker nasofaring di Poli THT -KL RSUP Prof. Dr. IGNG Ngoerah Denpasar pada tahun 2015. E-Jurnal Med. 2019;8(2):1–6.
23. Mo Y.L., Li L, Qin L, Zhu XD, Qu S, Liang X, et al. Cognitive function, mood, and sleep quality in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer: A prospective study. Psychooncology. 2014;23(10):1185–91.
24. Hartanto PD, Ketut N, Ariani P, Nyoman L, Aryani A. GAMBARAN TINGKAT KECEMASAN PADA PENDERITA KARSINOMA Program Studi Pendidikan Dokter , Fakultas Kedokteran Universitas Udayana Bagian Psikiatri Fakultas Kedokteran Universitas Udayana / Rumah Sakit Umum Pusat Prof. Dr. IGNG Ngoerah. 2019;8(6):1–9.
25. G. H-A, L. P, S.A. C-G, M.E. H, E. D-S, J. V-M. Sleep loss as a factor to induce cellular and molecular inflammatory variations. Clin Dev Immunol. 2013;2013:no pagination.
26. Coulon N, Brailly-Tabard S, Walter M, Tordjman S. Altered circadian patterns of salivary cortisol in individuals with schizophrenia: A critical literature review. J Physiol Paris. 2016;110(4):439–47. DOI: 10.1016/j.jphysparis.2017.05.002
27. Lee KC, Hsieh YL, Lin PC, Lin YP. Sleep Pattern and Predictors of Sleep Disturbance Among Family Caregivers of Terminal Ill Patients With Cancer in Taiwan: A Longitudinal Study. Am J Hosp Palliat Med. 2018;35(8):1109–17.
28. Pössel P, Mitchell AM, Harbison B, Fernandez-Botran GR. Repetitive Negative Thinking, Depressive Symptoms, and Cortisol in Cancer Caregivers and Noncaregivers. Oncol Nurs Forum. 2019;46(6):E202–10.
29. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020;14:1–14.

How to cite this article: I Gst Ayu Agung Aria Tristayanthi, Desak Ketut Indrasari Utami, I Made Oka Adnyana et.al. High C-Reactive Protein (CRP) levels as risk factors for poor sleep quality in patients with nasopharyngeal cancer with radiotherapy. *International Journal of Research and Review*. 2023; 10(4): 447-455. DOI: *https://doi.org/10.52403/ijrr.20230454*

******