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The Profile of P63 Expression and Epstein-Barr-Encoded RNA (EBER) Distribution in Primary Central Nervous System Lymphoma: A Retrospective Bi-Center Study

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Online First : February 2025

Abstract

Background : Primary central nervous system lymphoma (PCNSL) is a type of lymphoma occurring around 0.5 – 1.2% of all intracranial neoplasms. However, recent epidemiological research shows a threefold increase in the number of cases. The Epstein-Barr virus (EBV) and PCNSL are both associated with the condition of immunosuppression or immunodeficiency, which often found to have a significant relationship with each other. Moreover, the TP63 mutation is associated with a poor prognosis.

Methods : This is a descriptive study to assess the expression of TP63 and EBER on PCNSL, and present the characteristics of the disease. The study was conducted on 25 cases from two health centers with the most cases of brain tumors in Indonesia, Siloam Hospital Lippo Village and Cipto Mangunkusumo Hospital (CMH) from 2014 to 2018, the P63 expression and EBER-1 examinations were done by 4 pathologists. A total of 25 patients, 13 (52%) patients were male, ranging from age 30 – 79, with average 57,6 years old, located mostly in the frontal lobe in 8 patients (30.9%).

Result : From the research results obtained positive P63 results in 20 cases (80%), while the EBER test was negative for all 25 patients. Further analysis with software SPSS 25 proving that P63 expression is not associated with germinal center B-cell type (GCB) or non-GCB type (p-value 0,87). Neither, P63 have any association with Ki67 with p-value of 1.00.

Conclusions : This study concludes that there is a possibility that PCNSL cases in Indonesia are not associated with Epstein-Barr virus infection, but most of the cases will have a poor prognosis as indicated by P63 expression.

Introduction

Primary Central Nervous System Lymphoma (PCNSL) is an extra-nodal Non-Hodgkin Lymphoma.[1] It is a rare type of brain tumor, comprising only about 0.5 – 1.2% cases of intracranial neoplasms and <1% of extra-nodal non-Hodgkin's lymphoma.[2] Recent epidemiological research shows a threefold increase in the number of cases in the population.[3] PCNSL has a poorer prognosis compared to systemic lymphomas of the same subtype.[1]

The main risk factor for lymphoma of the central nervous system, both primary and secondary, is immunosuppression or immunodeficiency. HIV patients have a 3600-fold risk for PCNSL compared to the normal population.[2,4] PCNSL related to AIDS is also mainly associated with low CD4 cell counts (<50 cells/ L) and Epstein-Barr virus (EBV) infection.[2,4]

Other causes of lymphoid malignancies are genetic mutations, one of which is TP63. TP63 mutation and one of its loci, TBL1XR1, are also found in both B cell lymphoma and PCNSL.[5] The presence of TP63 and EBER on PCNSL might be the cause for poor prognosis. This is a descriptive study to assess the expression of TP63 and EBER on PCNSL and present the characteristics of the disease.

Material And Methods

Research Sample

This study was conducted with a cross-sectional study design. There was originally a total of 49 identified cases, however due to the specification of the data required, only 26 fulfilled the criteria. All 26 cases of PCNSL patients were taken from two health centers Siloam Hospital Lippo Village (SHLV) and Cipto Mangunkusumo Hospital (CMH) from the year of 2014 to 2018. The diagnostic criteria were reviewed by two pathologists (EK and SM).

PCNSL Patient Specimens

TP63 mutation examination was done with immunohistochemistry staining with P63 (Mouse Monoclonal Antibody, Biocare Medical, ready to use, catalogue number PM 163 AA, H). Positive control was done with prostate tissue while negative control was made by the absence of primary antibody. EBER-1 RNA examination was done with in situ hybridization (ISH) technique.

Immunohistochemistry staining of P63 were evaluated by two pathologists (EK and SM), with positive results with a value of more than 50% is declared as P63 positive, while ISH examinations were evaluated by 4 pathologists (EK, SM, AH and MH) altogether.

Data Analysis

The data was shown in descriptive model.

Result

Basic Characteristics of the Sample

Based on data from SHLV and CMH Anatomical Pathology Department Archives, the total number of samples that fulfilled the inclusion and exclusion criteria from 2014 to 2018 were 26 cases. Out of the 26 cases 16 cases were retrieved from SHLV, and 10 cases from CMH. From all samples, the mean age was 57 years old, with the youngest being 37 years old and the oldest 73 years old. The ratio between male and female patients was 1:1 (13 male and 13 female). The most common tumor location in this study was in the frontal region. (30.8%) (Table 1).

Table 1. Characteristics of the sample.

Characteristic	Category	Count	Percentage (%)
Gender	Male	13	50
	Female	13	50
Age	30-39	1	3.8
	40-49	5	19.2
	50-59	9	34.6
	60-69	7	27
	70-79	4	15.4
Location	Cerebrum	8	30.9
	Frontal	2	7.7
	Temporal	5	19.2
	Parietal	1	3.8
	Thalamic	1	3.8
	Corpus Callosum	3	11.5
	Cerebellum	6	23.1

Reassessment of PCNSL diagnosis includes morphologic and immunophenotypic features re-evaluation according to operational definitions. Morphological picture obtained showed a diffuse malignant lymphoid cell with large nuclei and prominent nucleoli, with plenty mitotic figures (Figure 1).

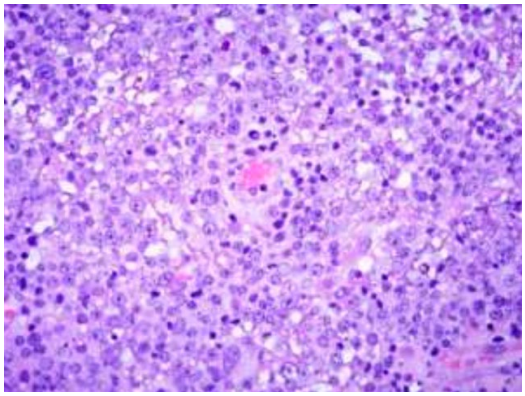

Figure 1. Primary Central Nervous Systems Lymphoma (PCNSL) Hematoxillin Eosin 400x.

After reassessing Hematoxylin and Eosin preparations, the study continued with reassessment of immunohistochemistry (IHC) results to confirm the diagnosis. During the IHC examination, a result of CD 20 positive was observed in all the cases. (Figure 2) From the IHC outline, a result of CD10 positive was found in 3 cases (11,5%) (Figure 3), MUM-1 positive in 24 cases (92.3%) (Figure 4), Bcl6 positive in 21 cases (80.8%) (Figure 5), and Ki- 67 positive on average of 74.1%. (Table 2) Based on the lymphoma molecular subtype by Han's criteria, there were 3 cases of the GCB group and 23 cases in the non-GCB group involved in this study.

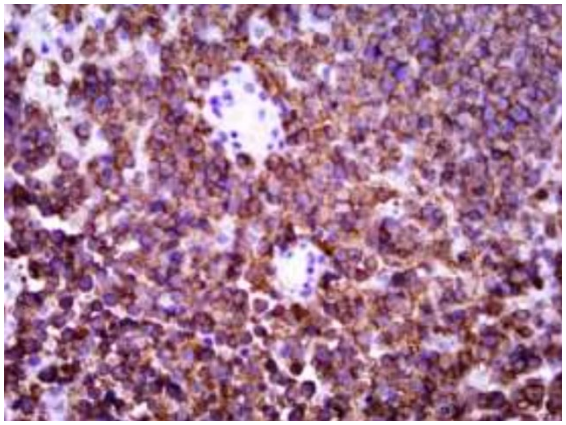

Figure 2. CD20 positive.

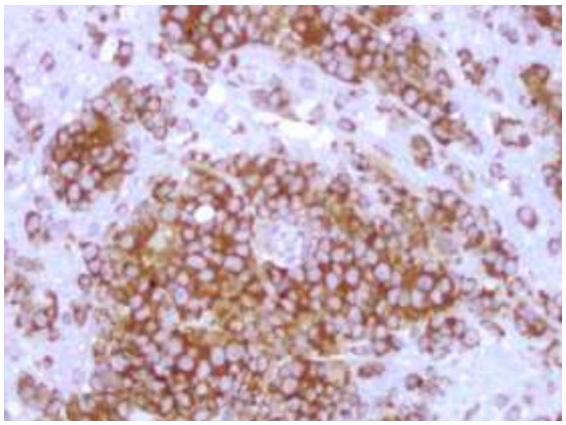

Figure 3. CD10 positive.

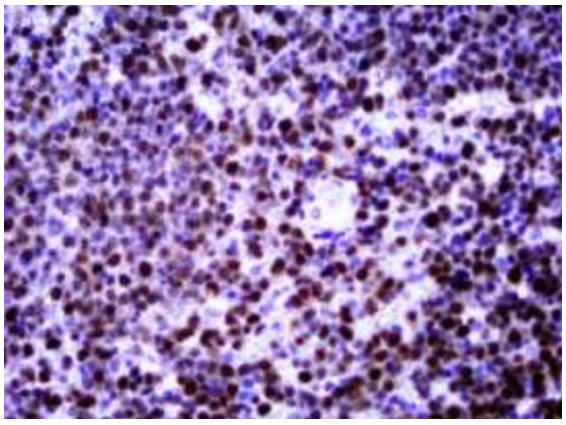

Figure 4. MUM1 positive.

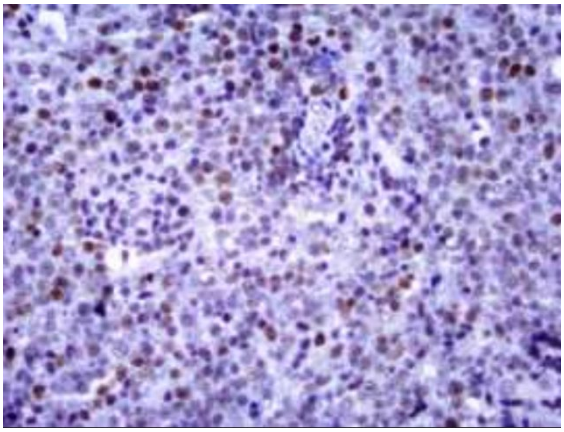

Figure 5. BCL6 positive.

Table 2. Antibody expression

Antibody Expression	Number of Cases Positivity	Percentage (%)
CD20	26.0	100
MUM-1	24.0	92.3
BCL6	21.0	80.8
P63	21.0	80.8
EBER-1 RNA (ISH)	0.0	0

Analysis of P63 and EBER expressions

P63 and EBER expressions assessment was done qualitatively. The test results were assessed by 2 researchers simultaneously. The results obtained showed a positive P63 expression in 21 cases (80.8%) (Figure 5), and EBER negative results were obtained from all cases (Figure 6). Because one of the variables obtained negative results in all cases, the correlation analysis test cannot be performed.

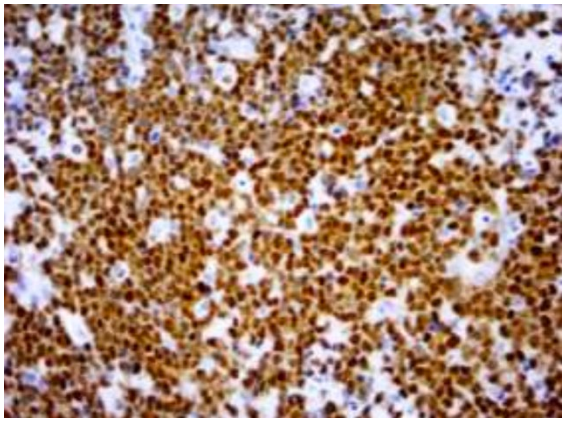

Figure 6. p63 positive.

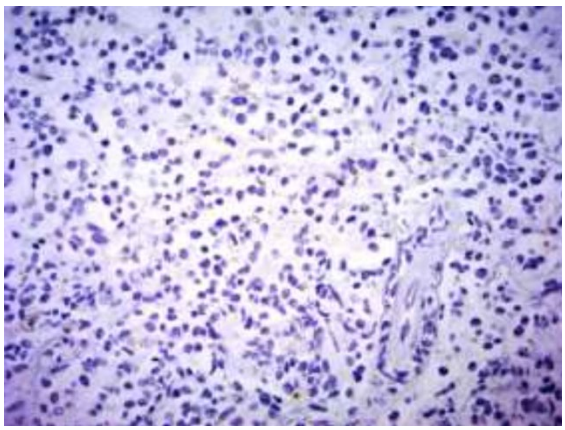

Figure 7. EBER negative.

Discussion

Basic Characteristics of Samples

The nature and findings of the study are placed in context of other relevant published data. Caveats to the study should be discussed. Avoid undue extrapolation from the study topic.

Primary central nervous system lymphoma (PCNSL) is an aggressive type of lymphoma that arises in the brain parenchyma, spinal cord, eyes, cranial nerves, and meninges. PCNSL patients involved in this study consisted of an equal ratio between men and women. This is consistent with the study conducted by Shiels et al, which shows the similarity in predominance between men and women in PCNSL cases in America.[6]

Primary central nervous system lymphoma (PCNSL) can occur in immune-competent individuals or immune-compromised individuals, including HIV-infected individuals and post-transplant patients. PCNSL is the main cause of morbidity and mortality in HIV-infected individuals before the advent of antiretroviral therapy. However, with the effective combination of antiretroviral therapy, the incidence of this disease begins to decrease.[2] Moreover, the incidence of PCNSL is increasing in HIV-negative individuals, where PCNSL is currently <1% of all non-Hodgkin's lymphoma (LNH) and around 2-3% of all brain tumors.[3]

About 90-95% of PCNSL is histologically classified as diffuse large B-cell lymphoma (DLBCL) which consistently expresses B cell antigens and has a generally positive MUM-1 and BCL-6, and only less than 10% express CD10.[3] Overall, PCNSL does not possess a molecular profile as in systemic DLBCL and B cell subtypes, but has a unique transcriptional description of gene expression profiling.[4] That is consistent with our study which showed that only 3 of the cases were CD10 positive.

PCNSL is a unique clinicopathological entity in DLBCL. PCNSL has a centroblastic morphology and originates from late germinal centre or early post germinal centre exit B cells. These cells have MUM-1 and BCL6 co-expression but not CD138. Thus, DLBCL PCNSL is different from systemic DLBCL because it cannot be classified into prognostic groups according to its cell origin. The prognostic effect of molecular changes remains to be determined. In addition, other things to note are the cell derivation and pathogenesis of DLBCL PCNSL.[6]

From a virology point of view, the DLBCL PCNSL contains an Epstein-Barr virus (EBV) infection, and can be detected in immune-compromised individuals.[4] In a study by Mahadevan, 24 patients with DLBCL PCNSL were analyzed in South India. These cases consistently showed centroblastic morphology and overall showed activated B-cell phenotype with MUM-1 expression, but not CD138. That study also showed BCL6 and MUM1 expression in 50% of cases. All cases were also negative for EBV with EBER in situ hybridization and latent membrane protein 1 (LMP1) immunohistochemistry. According to Mahadevan, patients with systemic DLBCL showed predominance of GCB origin in several studies and activated B-cell origin in several other studies.[6]

Because the CNS contains little lymph nodes and lymphatic vessels, there is a hypothesis that PCNSL can originate from B cells derived from systemic lymphoid tissue and normally circulates in and out of the CNS. The exact cell derivation is still unknown, and the pathogenesis of PCNSL is also still not well understood. The evidence currently available is only limited to the role of EBV in PCNSL relating to AIDS. Lymphoma cells in EBV infection often expresses encoded LMP-1 oncoprotein, which, in turn, upregulates the expression of BCL2. This suggests that EBV can act as an oncogenic agent or at least as an oncogenic cofactor.[7]

In contrast, EBV does not play a role in lymphomagenesis in immune-competent PCNSL patients. On genetic examination, immune-competent DLBCL PCNSL patients showed ongoing aberrant somatic hyper-mutation that, besides the IG locus, targets the PAX5, TTF, MYC, and PIM1 genes. Some important pathways are activated such as B-cell receptors (BCR), toll-like receptors, and nuclear factor-κB pathways. Genomic transitions on PCNSL include the loss of chromosome 6p21 which contains the locus of human leukocyte antigen (HLA).[6]

A case report in China reported that out of 9 cases, 2 presented with multiple lesions, while 7 patients exhibited a solitary lesion.[8] In this study, out of 26 cases, 6 cases reported to have multiple lesions, while 20 patients presented with solitary lesion. It is reported that around 34% of

PCNSL patients revealed multiple lesions.[9] These locations contribute to the symptoms occurred in patients.

The p63 gene, a homolog of the tumor suppressor gene TP53, maps to chromosome 3q27-28, a region frequently displaying genomic amplification in squamous cell carcinomas. In a study conducted by Cyrus et al, p63 expression was examined by immunohistochemistry using a monoclonal antibody (clone 4A4), while distinction of p63 isoforms was analyzed by Western blotting and reverse transcription-polymerase chain reaction using isoform-specific primers. The study found that a subset of DLBCL (32% of cases) expressed p63 in the nuclei of neoplastic lymphocytes. In this study, P63 was found in 84% of the cases, in which p63 is associated with high proliferative index, as assessed by Ki-67 immunostaining.[10]

A study in India, evaluating the Epstein-Barr virus as an etiology of PCNSL in immunocompetent individuals, found that ISH for EBER was negative in all 19 patients.[11] Th study concludes that in the region associated with this study, EBV likely has no etiologic role in the development of PCNSL in immunocompetent individuals. Correspondingly, EBER examination was found to be negative in all 26 patients involved in this study. However, a study regarding EBER in elderly patients on immunosuppressive medications by Kleinschmidt-DeMasters et al., found that in 4 patients examined positive for EBER, none of the patients develop symptoms of HIV-AIDS. These patients shown neuroimaging features typical for PCNSLS in immunocompromised patients (i.e. multifocal and ring-enhancing lesions).[12]

Conclusion

From this study, we confirm that most of the PCNSL are DLBCL non-GCB subtype, with p63 staining positive in 84% (21 cases) and all the cases we retrieved were EBER negative. According to the data we have collected most of the patients are 50 – 59 years old, consistent with the typical age associated with the occurrence of PCNSL. In HIV-AIDS patients, PCNSL tends to occur at a younger age and is associated with EBV infections. It is possible that the patients the researchers have gathered are HIV negative and therefore is not associated with EBV infections. Moreover, more data and examinations are needed to confirm the hypothesis. Nevertheless, it can be concluded that the demographic data in Siloam Hospital Lippo Village and Cipto Mangunkusumo Hospital both describing patients with PCNSL with EBER negative and therefore shows that EBV infection rate is low.

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(Erna Kristiani)

The Influence of The Severity of Obstructive Sleep Apnea on The Incidence of Hypertension

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Keywords: Obstructive Sleep Apnea (OSA); Hypertension; Severity; Polysomnography; Risk Factors.
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Online First : February 2025

Abstract

Background : Hypertension is a condition where systolic blood pressure reaches 140 mmHg, and diastolic blood pressure reaches 90 mmHg. According to the Ministry of Health of Republic Indonesia, hypertension ranks third as a cause of death in Indonesia. Secondary hypertension arises from identifiable causes such as obstructive sleep apnea, renal vascular disease, hormonal contraceptives, endocrine disorders, stress-induced hypertension, pregnancy, burns, renal parenchymal disease, polycystic ovarian syndrome, preeclampsia, and specific medications like NSAIDs and antidepressants. Previous studies have recorded 83% Hypertension patients had OSA. Despite these findings, there are still contradictions in the literature (7), indicating the need for further research to explore the relationship between OSA and hypertension, as well as the impact of different types of OSA on hypertension.

Methods : This research is an observational analytic study using a cross-sectional method. Medical status data and polysomnography results were collected from February to April 2024 at Siloam Hospitals Lippo Village. Data were processed using SPSS 23.0 and analyzed using the chi-square method. Significant variables will be further analyzed using logistic multivariate analysis.

Result : There was an influence of the severity of Obstructive Sleep Apnea on the incidence of hypertension at Siloam Hospitals Lippo Village (OR=15.4, 95%CI 3.477 – 68.216; p-value=0.001). Besides the influence of the severity of Obstructive Sleep Apnea, other variables such as gender, BMI ≥ 23 kg/m², and a history of diabetes mellitus also affected the incidence of hypertension.

Conclusion : The influence of the severity of Obstructive Sleep Apnea on the incidence of hypertension found in Siloam Hospitals Lippo Village.

Introduction

Hypertension, defined by the World Health Organization (WHO) as a condition where systolic blood pressure reaches or exceeds 140 mmHg and diastolic blood pressure reaches or exceeds 90 mmHg,[1] predominantly affects the elderly but can occur across all age groups. In 2018, WHO reported that approximately 972 million individuals, constituting about 26.4% of the global population, were diagnosed with hypertension—a figure that continues to rise annually, reaching 29.2% by 2021. Globally, hypertension contributes to an

estimated 9.4 million deaths annually. In Indonesia, hypertension ranks third as a cause of death after stroke and tuberculosis.[2] With a prevalence of 34.11%, Indonesia is fifth globally in hypertension cases, and this prevalence is expected to escalate, potentially affecting 1.5 billion individuals by 2025. Essential hypertension, which comprises around 90% of cases, lacks a clear identifiable cause, though several contributing factors have been identified. These include genetic predisposition, insulin resistance, gender, high salt and fat diet, advanced age, sedentary lifestyle, low potassium and calcium intake, obesity, smoking, alcohol consumption, and imbalances in vasodilation and vasoconstriction modulators. Additionally, the Renin-Angiotensin-Aldosterone System (RAAS) and sympathetic nervous system play significant roles in hypertension development.[3] In contrast, secondary hypertension arises from identifiable causes such as obstructive sleep apnea, renal vascular disease, hormonal contraceptives, endocrine disorders, stress-induced hypertension, pregnancy, burns, renal parenchymal disease, polycystic ovarian syndrome, preeclampsia, and specific medications like NSAIDs and antidepressants.[4]

Obstructive Sleep Apnea (OSA), characterized by recurrent upper airway collapse during sleep leading to decreased oxygen saturation and fragmented sleep, is classified by severity based on the apnea-hypopnea index (AHI). Mild OSA ranges from 5 to 15 AHI, moderate from 15 to 30, and severe exceeds 30.[5] The condition is associated with increased sympathetic nervous system activity due to repeated airway obstruction, potentially contributing to hypertension development. Research in Indonesia indicates an 83% prevalence of OSA and hypertension among study participants, despite these findings, there are still contradictions in the literature,[7] indicating the need for further research to explore the relationship between OSA and hypertension, as well as the impact of different types of OSA on hypertension.

To address these issues, our study aims to investigate the relationship between Obstructive Sleep Apnea severity and hypertension incidence at Siloam Hospitals Lippo Village, Tangerang. As well as the impact of different types of OSA on hypertension. Understanding these interconnections could provide valuable insights into managing and preventing hypertension, particularly in populations affected by OSA.

Material And Methods

This study has been approved by the Ethics Committee of Faculty of Medicine, Pelita Harapan University with the approval number 019/K-LKJ/ETIK/2024.

Participants and Study Design

This study adopts an analytical research design, specifically employing a quantitative approach with a cross-sectional method to investigate the impact of Obstructive Sleep Apnea severity on hypertension. 52 data were obtained from patients suspected of having obstructive sleep apnea (OSA) at Siloam Hospital in Lippo Village from January to December 2022. Then data were sorted based on the inclusion and exclusion criteria, which are inclusion critreria; patients of Siloam Hospitals Lippo Village 2022, Patients who have polysomnography results, AHI ≥ 5 and exclusion criteria which are; history of Continuous Positive Airway Pressure usage, history of kidney disease and Stroke history. 4 samples were excluded, 2 of which did not have polysomnography results, and 2 among them had a history of CPAP use. As a result, the final number of research samples was 48.

Operational Definition

The severity of OSA was assessed using the AHI, a metric calculated from polysomnography that quantified the hourly occurrence of respiratory disturbances during sleep. Cases were classified as mild (5–14.9 episodes/hour) or moderate-severe (>15 episodes/hour). Hypertension was defined by systolic blood pressure measurements of ≥140 mmHg and/or diastolic values of ≥90 mmHg, or documented administration of antihypertensive agents such as diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors. Age was recorded as a continuous variable representing years since birth, while Diabetes Mellitus was identified through clinical confirmation of impaired glycemic regulation. Overweight status adhered to the Asia-Pacific classification, determined by a BMI of ≥23 kg/m² derived from anthropometric data. Gender was categorized dichotomously as male or female. All variables were systematically extracted from clinical documentation to standardize data collection.

Statistical Analysis

Data collection will be conducted using medical status and polysomnography. Data analyzed using SPSS 23.0. The research data will be tested using the chi-square method to examine the independent factor (OSA) and the dependent factor (Hypertension). In this research confounding variables (age, gender, history of Diabetes Melitus and BMI ≥ 23 kg/m²) will be further analyzed using logistic multivariate analysis.

Result

From a total of 52 samples with indications of obstructive sleep apnea were collected, which were then selected based on inclusion criteria. Four samples were excluded: two due to lack of polysomnography results and two due to a

history of CPAP usage. The final sample size for the study was 48 samples.

Table 1. Sample Characteristics

Sample Characteristics	(n%)
Gender	
Men	37 (71.1%)
Women	11 (22.9%)
Age (year)	
≥60	9 (18.8%)
<60	39 (81.3%)
Body Mass Index (Kg/m²)	
≥ 23 Kg/m²	34 (70.8%)
< 23 Kg/m²	14 (29.2%)
Apnea Hypopnea Index	
Moderate-Severe	32 (66.7%)
Mild	16 (33.3%)
Hypertension Status	
Yes	33 (68.8%)
No	15 (31.3%)
History Diabetes Mellitus	
Yes	31 (64.6%)
No	17 (35.4%)

The majority of samples were male, comprising 77.1%, aged < 60 years at 81.3%, with BMI ≥ 23 kg/m² at 70.8%, having a history of Diabetes Mellitus at 64.6%, exhibiting moderate to severe AHI status at 66.7%, and having hypertension at 68.8%.

Association of Severity Obstructive Sleep Apnea and Hypertension

Table 2. Association of Severity Obstructive Sleep Apnea and Hypertension

Hypertension Status and Related Factors	Yes n (%)	No n (%)	Total	OR	OR (95% CI, P)	P
Apnea Hypopnea Index						
Moderate-Severe	28 (84.8%)	5 (15.2%)	33	15.4	(3.477-68.216, 0.001)	0.001
Mild	4 (26.7%)	11 (73.3%)	15			
Gender						
Men	31 (93.9%)	6 (40%)	37	23.25	(3.984-135.682, 0.001)	0.001
Women	2 (6.1%)	9 (60%)	11			
BMI						
≥23 Kg/m²	31 (93.9%)	7 (46.7%)	38	17.71	(3.069-102.262, 0.001)	0.001
<23 Kg/m²	2 (6.1%)	8 (53.3%)	10			
Age						
≥60	7 (77.8%)	2 (22.2%)	9	1.750	(0.318-9.644, 0.803)	0.803
<60	26 (66.7%)	13 (33.3%)	39			
History Diabetes Mellitus						
Yes	28 (84.8%)	3 (20%)	31	22.4	(4.600-109.085, 0.001)	0.001
No	5 (15.2%)	12 (80%)	17			

Association between Apnea Hypopnea Index and Hypertension Status

In this study, 28 samples with moderate-severe AHI were found to have hypertension. Conversely, only 4 samples with mild AHI had hypertension. Based on the chi-square test examining the relationship between Apnea Hypopnea Index and hypertension, a Crude Odds Ratio of 15.4 was obtained. This indicates that subjects with moderate-severe Obstructive Sleep Apnea are 15.4 times more likely to experience hypertension compared to those with mild Obstructive Sleep Apnea, and the relationship between the severity of Obstructive Sleep Apnea and hypertension incidence is statistically significant (p-value = 0.001).

Association between Gender and Hypertension Status

In this study, 31 male samples were found to have hypertension. Conversely, only 2 female samples had hypertension. Based on the chi-square test examining the relationship between gender and

hypertension, a Crude Odds Ratio of 23.25 was obtained. This indicates that males are 23.25 times more likely to experience hypertension compared to females, and the relationship between gender and hypertension status is statistically significant (p-value = 0.001).

Association between BMI and Hypertension Status

In this study, 31 samples with BMI ≥ 23 kg/m² were found to have hypertension. Conversely, only 2 samples with BMI < 23 kg/m² had hypertension. Based on the chi-square test examining the relationship between BMI and hypertension, a Crude Odds Ratio of 17.71 was obtained. This indicates that subjects with BMI ≥ 23 kg/m² are 17.71 times more likely to experience hypertension compared to those with BMI < 23 kg/m², and the relationship between BMI and hypertension incidence is statistically significant (p-value = 0.001).

Association between Age and Hypertension Status

In this study, 7 samples aged ≥ 60 years were found to have hypertension. Conversely, 28 samples aged < 60 years had hypertension. Based on the chi-square test examining the relationship between age and hypertension, a Crude Odds Ratio of 1.7 was obtained. However, the Crude Odds Ratio result was not statistically significant (p-value = 0.803).

Association between History of Diabetes Mellitus and Hypertension Status

In this study, 28 samples with a history of Diabetes Mellitus also had hypertension.

Conversely, only 5 samples without a history of Diabetes Mellitus had hypertension. Based on the chi-square test examining the relationship between Diabetes Mellitus history and hypertension, a Crude Odds Ratio of 22.4 was obtained. This indicates that subjects with a history of Diabetes Mellitus are 22.4 times more likely to experience hypertension compared to those without a history of Diabetes Mellitus, and the relationship between Diabetes Mellitus history and hypertension incidence is statistically significant (p-value = 0.001).

Table 3. Multivariate Analysis Results

	Adjusted Odd Ratio	95% CI	P-value
Severity of OSA	4.53	1.312-605	0.033
Gender	5.39	1.751-735.8	0.02
BMI	4.44	1.378-6466	0.035
History of Diabetes Melitus	4.25	1.198-1149	0.039

In the multivariate logistic regression analysis, after adjusting for other variables, the severity of AHI remained associated with hypertension. The difference between the Crude Odds Ratio and the Adjusted Odds Ratio exceeded 10% for gender, BMI, and history of Diabetes Mellitus, indicating that these variables acted as confounders in this study. Additionally, gender, BMI, and history of Diabetes Mellitus were statistically significant (p-value < 0.05).

Discussion

In this study, the patient sample consisted of 77% males and 23% females. The majority of the sample had moderate-severe AHI, comprising 32 subjects out of a total of 48. A study by Michel showed a similar distribution with 60.2% male and 39.8% female participants, and a majority of 70.6% had moderate-severe AHI.[7] Regarding hypertension status, 68.8% of the participants had hypertension, with 19% aged ≥60 years and 81% aged <60 years. This distribution is like the findings of Yunua, where 80% of the sample was aged <60 years and 20% aged ≥60 years, with 70% having hypertension.[8] In this study, 70.8% of the subjects had BMI > 23 and 29.2% had BMI < 23, and 64.6% had a history of diabetes mellitus. Studies by Tince and Jung Hwan Jo also showed a similar distribution with 20% of patients having a BMI < 23 and 65% having a history of diabetes mellitus.[9,10]

In this study, the severity of OSA was divided into two groups: mild and moderate-severe. Due to the small number of samples (severe = 6), the severe cases were combined with the moderate cases for analysis. The study found that the severity level of AHI > 15 was associated with a higher risk of hypertension, cardiovascular disease, and other health problems. This division also allowed researchers to focus on more severe cases of OSA, which are more likely to have a significant impact on the health and quality of life of patients. In this study, 66.7% of subjects had moderate-severe OSA and 33.3% had Mild OSA. In the analysis of the strength of the relationship, it was found that the severity of OSA severity had a strong association with the incidence of hypertension. This was evidenced by a crude OR of 15.4 with a p-value of 0.001, and an OR after controlling for gender, history of diabetes mellitus, and BMI still showed significant results (AOR = 4.53; p-value = 0.033). Studies by Grote et al. and Youte et al., which discussed the influence of the severity of OSA on the incidence of hypertension, also found a significant relationship with the severity of OSA on the incidence of hypertension, as evidenced by an increased OR found in Parati et al., obtained an OR of 6.84 for Moderate-Severe OSA with hypertension,[11] and in the study by Young found an increase in the incidence of hypertension, in mild OSA by 57% and 67% of moderate-severe OSA.[12] This is also supported by physiological theories, OSA can cause an increase in blood pressure due to increased sympathetic nervous activity, increased RAAS activity, and oxidative stress due to hypoxia conditions that occur during sleep.

Older age can influence the occurrence of OSA. According to Osorio et al., 50% of OSA cases occur in individuals aged ≥60 years, attributed to lax throat tissues and muscles causing increased pharyngeal resistance. Individuals aged

≥60 years tend to experience easier weight gain due to decreased physical activity and growth hormone, which subsequently increases fat accumulation by reducing lipolysis. Moreover, decreased sensitivity to thyroid hormones and leptin resistance contribute to decreased appetite suppression. This is one of the reasons why OSA is more prevalent in those aged ≥60 years. However, this study found that individuals aged <60 years' experience OSA more frequently than those aged ≥60 years. This finding aligns with Edward et al.'s research, suggesting it may be due to subjects aged ≥60 years having a tendency towards a non-overweight BMI. Hypertension is also more prevalent in those aged ≥60 years, as studies show that after the age of 60, the inhibitory effect of L-NMMA on acetylcholine response is weak, and Nitric Oxide availability is completely disrupted in the elderly population.[13-15]

In this study age groups were divided into <60 years and ≥60 years. According to RISKESDAS in 2018, 63.2% of those aged ≥60 years were found to have hypertension.[16,17] This is physiologically due to a decline in nitric oxide levels at 60 years of age. Nitric oxide is produced from the precursor L-Arginine, which is converted into nitric oxide with the help of Nitric Oxide Synthase enzymes, catalyzing the oxidation of five electrons from guanidino nitrogen L-arginine. However, in those aged ≥60 years, most studies on NO activity in cells and tissues agree that biological availability or generation of NO from NOS decreases with age. Vascular changes related to hypertension, such as endothelial dysfunction, accelerate with aging.[18-20] Additionally, the presence of acetylcholine along with NO synthase inhibitor (L-NMMA) was tested for NO availability in blood vessels. After the age of 60, the inhibitory effect of L-NMMA on acetylcholine response is very weak, indicating that NO availability is completely disrupted in the elderly population. Studies also indicate that subjects aged 60 years show decreased sensitivity in taste senses, especially to salty tastes, leading to increased use of flavor enhancers and high salt in consumed foods, which further increases the incidence of hypertension.[13]

In this study, subjects aged ≥60 years accounted for 18.8%, and <60 years accounted for 81.3%. Regarding the relationship, this study found that age ≥60 years is not associated with the occurrence of hypertension, although the crude OR obtained was 1.4, the OR obtained was not statistically significant (p-value = 0.8). The findings of the crude OR cannot indicate a relationship and may occur by chance. These findings do not align with physiological theories and other studies investigating sociodemographic factors influencing hypertension in aging. Studies by Etrin et al. and Aida et al. state that there is a significant relationship between age ≥60 years and the occurrence of hypertension. In Erin et al.'s study involving

757 samples and Aida et al. study involving 5,874 samples, Erin et al. obtained an adjusted odds ratio of 28.1 for age over 60 years with a p-value = 0.002, and Lydia et al. obtained a p-value of 0.001 after comparison with other variables and an adjusted odds ratio of 1.68. Both findings indicate that age ≥60 years has a higher risk compared to age <60 years for the occurrence of hypertension.[21,22] These findings are consistent with a study from Brazil that found age <60 years increases the risk of hypertension.[23] This is hypothesized to occur because subjects aged ≥60 years in the study had a better BMI compared to those aged <60 years. Additionally, this finding may be due to uneven age distribution, so subjects aged ≥60 years tend to be unrelated to the occurrence of hypertension (p-value = 0.803).

In this study, 24 OSA subjects were found to have diabetes mellitus. Diabetes mellitus and OSA have a significant relationship, but this does not imply that OSA is the cause of diabetes; it can be bidirectional and overlap. In a study by Mok et al., involving 30 patients with diabetes mellitus, glycemic control was performed, and after 5 days, there was a reduction in the severity of obstructive sleep apnea. Tince et al. also suggest that diabetes mellitus can cause OSA through mechanisms involving muscle tone reduction. Diabetes can cause nerve damage (neuropathy) that controls the muscles around the pharynx, leading to weakness and vulnerability to collapse during sleep. The study found a statistically significant relationship (p-value 0.045). Other studies also found that obstructive sleep apnea can worsen diabetes mellitus through intermittent hypoxia, which increases sympathetic activity and leads to chronic oxidative stress and inflammation. This contributes to glucose metabolism disorders. The adverse effects of hypoxia can also directly affect the function of pancreatic beta cells, liver, and adipose tissue, all of which are involved in glucose homeostasis.[24-26]

In this study, a significant relationship was found between diabetes mellitus and hypertension, with a crude OR of 22.4 and an OR adjusted for OSA severity, gender, and history of diabetes mellitus of 4.25, and this relationship is statistically significant (p < 0.05).In theory, diabetes mellitus is related to hypertension through insulin resistance, which increases sympathetic nerve activity, endothelial dysfunction, sodium and water resistance, increased RAAS activity, and increased production of clotting factors and inflammatory mediators that can damage blood vessels.[27] Studies by Guanghong et al. and Prisilia et al., examining the relationship between diabetes mellitus and hypertension, found that diabetes mellitus can increase the incidence of hypertension.[28] Jia et al. study found that 80% of subjects with diabetes

mellitus had hypertension and had a 2- to 4-fold increased risk of hypertension.[29]

In this study, 28 OSA subjects had a BMI ≥23 kg/m². Jo et al. in Korea found that a BMI ≥23 kg/m² is associated with OSA. Jehan et al. in America found different results, showing that a BMI ≥25 kg/m² is associated with OSA. These differing findings may be due to ethnic differences. In Asian populations, BMI associated with OSA is lower compared to Caucasian populations, possibly due to smaller jaw size and higher airway collapsibility.[30,31] BMI in this study was divided into two groups: BMI ≥23 kg/m² and BMI < 23 kg/m² because BMI ≥23 kg/m² is considered the BMI threshold for hypertension risk defined by the Asia-Pacific region, specifically for Asia. However, only one study has researched cut-off points at a BMI of 22.4 kg/m², which is considered suitable for Indonesia. This lower threshold compared to Europe is due to the tendency of Asian populations to have a higher body fat percentage with a lower BMI compared to European populations. This is known as the Yudkin-Yajnik (Y-Y) paradox. Differences in body composition are thought to be related to a higher body fat percentage and prevalence of abdominal obesity in Asian populations, thereby increasing the risk of hypertension.[32-34]

In this study, 70.8% of subjects had a BMI ≥23 kg/m² and 29.2% had a BMI < 23 kg/m². In terms of strength of the relationship, BMI has a strong association with the occurrence of hypertension, as seen in the crude OR of 17.71 and the OR adjusted for OSA severity, gender, and history of diabetes mellitus of 4.44, and this relationship is statistically significant ($p < 0.05$).

In theory, BMI is related to hypertension through activation of the sympathetic nervous system, intra-abdominal and intra-vascular fat amounts, kidney sodium retention leading to increased reabsorption, changes in cytokine derivatives (leptin and hyperinsulinemia), and renin-angiotensin system, which are considered to play an important role in the pathogenesis of obesity-related hypertension.[35] Studies by Hong Seok Lee et al., Fariha et al., and Asyafah et al., looking at the relationship between BMI ≥23 kg/m² and hypertension, found that BMI is significantly associated with hypertension. All three studies also found that subjects with BMI ≥23 kg/m² had an increased risk of hypertension and found a p-value <0.05, further demonstrating the strong association between BMI ≥23 kg/m² and hypertension.[36,37]

In this study, 28 samples with OSA were found to be male. Men have a higher prevalence of OSA compared to women, with a study explaining that the prevalence ratio of men affected by OSA compared to women is as high as 3:1. This is due to physiological differences where estrogen

can help maintain airway patency by increasing upper respiratory muscle activity and differences in fat distribution (in males, fat distribution is visceral, whereas in females, it is peripheral; visceral fat accumulation around the neck and chest can compress the airway, especially during sleep when throat muscles relax). Pressure from visceral fat can narrow or block the airway, triggering apnea episodes or reduced airflow during sleep. The length of the upper respiratory tract is found to be higher in males than in females, which is associated with a higher tendency for airway collapse. In the study by Duarte et al., it was found that being male is associated with the occurrence of OSA (p-value <0.001).[38] In this study, there were 37 male subjects and 11 female subjects. Regarding their relationship, it turns out that being male has a strong association with the occurrence of hypertension, as seen from the crude OR of 23 and the OR adjusted for OSA severity, history of diabetes mellitus, and BMI of 5.3, which is statistically significant (p <0.05).

In theory, males tend to have a higher incidence of hypertension compared to females. However, when females reach menopause, estrogen levels tend to decrease, and the risk of hypertension becomes similar to that of males. Estrogen can stimulate the production of nitric oxide (NO), which is a protective mechanism against hypertension. Nitric oxide is a naturally produced vasodilator that controls vascular tone and thus regulates blood pressure. However, menopause does not have a precise age range but generally begins around age 45 and ends around age 65.[39,40]

Research by Falah et al. and Deffiana et al., examining sociodemographic factors influencing the occurrence of hypertension, found that hypertension is more likely to occur in males. Deffiana et al.'s study in Indonesia showed that males have an increased risk of hypertension compared to females.[41,42] However, in a study by Kusumawaty et al., a comparison found that 58% were females and 42% were males suffering from hypertension. These differing findings are due to the age of the population used in the study. The subjects used in the study were mostly over 60 years old.[43] As explained earlier, women over the age of 60 experience menopause, which ultimately leads to estrogen loss, reducing the risk factor for hypertension.

Multivariate Analysis

Multivariate analysis was conducted to determine whether variables that were found to be significant in bivariate testing maintained their significance when controlled for other variables. Variable selection was performed after bivariate analysis, focusing on variables with P-values ≤ 0.25. These variables were further analyzed using multivariate logistic

regression analysis. They were considered suitable candidates for inclusion in the multivariate logistic regression analysis. The candidate variables for analysis included the severity of OSA, gender, BMI, and history of diabetes mellitus.

In the multivariate analysis, gender was found to be the most significant variable contributing to hypertension. This may be due to most of the samples being male, with hypertension more likely to occur in males than females. Additionally, the severity of OSA was observed to still be associated with hypertension. The crude odds ratio obtained was 15.4, which changed to 4.53 after controlling other variables. The difference in OR values is hypothesized to be because each variable included in the multivariate analysis has a strong relationship and acts as a confounding factor. Gender, severity of OSA, BMI, and history of diabetes mellitus were identified as confounding factors, evidenced by the difference in crude OR and adjusted OR >10% for these variables. OR >1 obtained for gender, severity of OSA, BMI, and history of diabetes mellitus indicates a statistically significant association with hypertension (p-value <0.05).

Strengths and Limitations of the Study

Based on the data and discussions provided, obstructive sleep apnea (OSA) being one of the contributing factors. Studies have established a link between OSA and hypertension. While studies have established a link between OSA and hypertension, some research shows conflicting results and does not thoroughly explore the impact of OSA severity on hypertension incidence. Therefore, this study's focus on OSA severity is a significant strength. Additionally, this study employed multivariate analysis to assess the strength of the relationship between OSA and hypertension after controlling other variables. However, a notable limitation of this study is the small sample size, which may impact on the generalizability of the findings and reduce the statistical power of the analysis.

Conclusion

In conclusion, there is a significant influence of the severity of Obstructive Sleep Apnea (OSA) on the occurrence of hypertension at Siloam Hospitals Lippo Village, after adjusting for the three variables.

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COX-2 Expression and Its Prognostic Implications in Uterine Leiomyosarcoma: A Systematic Review and Meta-Analysis

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Abstract

Background : Uterine leiomyosarcoma (ULMS) is a rare, aggressive malignancy with high recurrence and poor survival, necessitating prognostic biomarkers and therapeutic targets. Cyclooxygenase-2 (COX-2), implicated in tumorigenesis and angiogenesis, remains understudied in ULMS. This systematic review and meta-analysis assessed COX-2's prognostic role in ULMS.

Methods : Following PRISMA guidelines, six studies (n=185) were retrieved from PubMed, EMBASE, and Scopus (2001–2024). Inclusion criteria required ULMS cohorts with COX-2 expression data and survival outcomes. Risk of bias was assessed using QUADAS-2, and evidence certainty via GRADE. A random-effects meta-analysis calculated pooled effect estimates with 95% confidence intervals (CIs), while heterogeneity was evaluated using I^2 statistics.\

Result : COX-2 expression correlated moderately with epithelial components (pooled effect: 0.51, 95% CI: 0.26–0.77) and weakly with mesenchymal components (0.26, 95% CI: 0.06–0.45). High heterogeneity (I^2 = 89.5% and 82.2%) reflected differences in study design, tumor subtypes, and COX-2 measurement thresholds. QUADAS-2 indicated a low risk of bias, and GRADE confirmed high evidence certainty. Stronger epithelial correlations were observed in Asian cohorts, highlighting geographic variability.
Conclusions: COX-2 plays a more significant role in epithelial-driven ULMS carcinogenesis. Despite heterogeneity, robust methodologies support these findings. Future studies should standardize COX-2 assessment, expand cohort sizes, and integrate multi-omics approaches to refine prognostic and therapeutic applications.

Introduction

Uterine leiomyosarcoma (ULMS) is a rare but aggressive mesenchymal malignancy arising from the smooth muscle of the uterus.[1] Despite accounting for only a small fraction of uterine cancers, ULMS poses significant clinical challenges due to

its high recurrence rates, propensity for metastasis, and poor overall survival outcomes.[2] The molecular mechanisms underlying its pathogenesis remain incompletely understood, necessitating further research into biomarkers and therapeutic targets to improve prognostic predictions and treatment strategies.

Cyclooxygenase-2 (COX-2) is a key enzyme in the conversion of arachidonic acid to prostaglandins, playing critical roles in inflammation, tumorigenesis, and angiogenesis.[3] Aberrant COX-2 expression has been implicated in various epithelial and mesenchymal malignancies, including breast, colorectal, and soft tissue sarcomas. In epithelial tumors, COX-2 overexpression is often associated with enhanced tumor cell proliferation, resistance to apoptosis, and immune evasion.[4,5] Similarly, in mesenchymal tumors, COX-2 contributes to tumor progression through mechanisms such as angiogenesis, extracellular matrix remodeling, and immune modulation. However, the exact role of COX-2 in the pathogenesis of ULMS remains less well characterized.

The potential prognostic value of COX-2 expression in ULMS is an area of growing interest. Previous studies have demonstrated varying levels of COX-2 expression in ULMS, with some suggesting associations between COX-2 overexpression and adverse clinical outcomes such as reduced progression free survival (PFS) and overall survival (OS).[6–8] However, the findings across studies have been inconsistent, likely due to differences in sample sizes, methodologies, and analytical approaches. These inconsistencies underscore the need for a systematic review and meta-analysis to synthesize existing evidence and provide a more definitive understanding of the relationship between COX-2 expression and ULMS prognosis.

Identifying reliable prognostic biomarkers in ULMS is critical for risk stratification, personalized treatment planning, and the development of targeted therapies. COX-2, as a modifiable biomarker, holds promise not only for prognostication but also as a potential therapeutic target.[9] Selective COX-2 inhibitors have shown antitumor activity in preclinical models and some clinical settings, highlighting their relevance in cancer treatment. A comprehensive evaluation of COX-2's prognostic implications in ULMS could pave the way for future translational research and clinical trials aimed at improving outcomes for patients with this challenging malignancy.[10]

Material And Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[11] The current study protocol was available online on PROSPERO. A structured PICO

framework guided the research, focusing on patients diagnosed with uterine leiomyosarcoma (Population), analyzing COX-2 expression (Intervention), comparing COX-2 expression levels between different cell types such as mesenchymal and epithelial (Comparator), and measuring primary outcomes of COX-2 expression levels in tissue level – epithelial and mesenchyme (Outcomes). Comprehensive searches were conducted in PubMed, EMBASE, and Scopus for studies published up to January 10, 2025, using combinations of keywords and Medical Subject Headings (MeSH) terms related to “COX-2,” “cyclooxygenase-2,” “uterine leiomyosarcoma,” “prognosis,” and “survival.” No language restrictions were applied (**Table 1**).

Table 1. Search strategy applied in different databases to retrieve potential literature.

Academic database	Search queries applied
PubMed	("cyclooxygenase 2"[MeSH Terms] OR "cyclooxygenase 2"[All Fields] OR "COX-2"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields] OR ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields])) AND ("uterin"[All Fields] OR "uterines"[All Fields] OR "uterus"[MeSH Terms] OR "uterus"[All Fields] OR "uterine"[All Fields]) AND ("leiomyosarcoma"[MeSH Terms] OR "leiomyosarcoma"[All Fields] OR "leiomyosarcomas"[All Fields] OR ("carcinosarcoma"[MeSH Terms] OR "carcinosarcoma"[All Fields] OR "carcinosarcomas"[All Fields]) OR ("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma s"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]))
EMBASE	cyclooxygenase-2 OR cox-2 AND prognosis OR survival AND uterine AND leiomyosarcoma OR carcinosarcoma OR sarcoma OR tumors OR cancers OR neoplasm
Scopus	cyclooxygenase-2 OR cox-2 AND prognosis OR survival AND uterine AND leiomyosarcoma OR carcinosarcoma OR sarcoma OR tumors OR cancers OR neoplasm

The inclusion criteria for the review consisted of studies reporting COX-2 expression in uterine leiomyosarcoma, studies providing data on clinical outcomes such as survival analysis, and original research articles, including cohort, case-control, or cross-sectional studies. Studies were excluded if they were non-original articles (e.g., reviews, editorials, or case reports), lacked clear data on COX-2 expression or clinical outcomes, or were animal or in vitro studies without patient data.

Two independent reviewers will extract data using a standardized data collection

form, with discrepancies resolved through discussion or consultation with a third reviewer. Extracted data will include study characteristics (e.g., author, publication year, study design, sample size, and geographical location), patient characteristics (e.g., age, sex, tumor stage, and histological subtype), COX-2 expression details (e.g., method of detection, expression levels, and categorization).

In this systematic review, the quality and certainty of the included studies were meticulously evaluated using the QUADAS-2 and GRADE frameworks. The QUADAS-2 tool, designed to assess diagnostic accuracy studies, examines four critical domains: patient selection, the index test, the reference standard, and flow and timing. This structured assessment identifies potential biases while ensuring the studies' relevance to the core research question. Complementing this, the GRADE system was utilized to determine the certainty of evidence across outcomes. By addressing key factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias, GRADE assigns confidence levels ranging from very low to high, offering a nuanced understanding of the strength of the evidence base.

The statistical analysis was conducted using RStudio and the meta package to perform a meta-analysis of proportions. A random-effects model was employed irrespective of the degree of heterogeneity to account for potential variability between studies. Pooled proportions were calculated along with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic to quantify the proportion of variability due to between-study differences, with statistical significance defined as a p-value < 0.05. To evaluate potential publication bias, a funnel plot was constructed for visual inspection, and Begg's and Egger's tests were applied to statistically assess funnel plot asymmetry. Forest plots were generated to illustrate the individual study estimates, pooled effect sizes, confidence intervals, and heterogeneity measures in a comprehensive manner.

Result

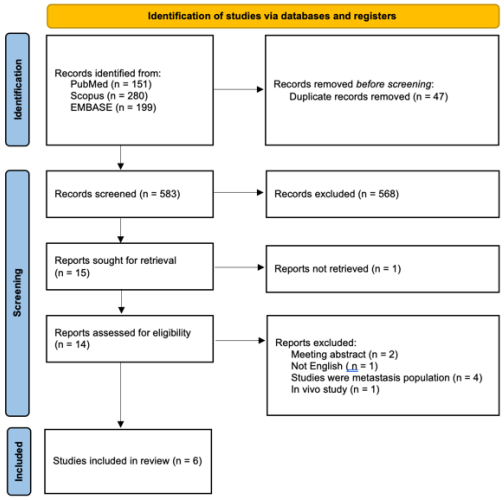

Figure 1. PRISMA flow diagram of the study selection process.

This systematic review began with the identification of 583 records from various databases: PubMed (n = 151), Scopus (n = 280), and EMBASE (n = 199) (**Figure 1**).

After removing 47 duplicate records prior to screening, 536 unique records were screened. Of these, 568 were excluded during the initial review. Subsequently, 15 reports were sought for retrieval, but one report could not be retrieved. After retrieval, 14 reports were assessed for eligibility. Eight reports were excluded for the following reasons: two were meeting abstracts, one was not in English, four focused on a metastasis population, and one was an in vivo study. Ultimately, six studies were included in the systematic review.[12–17]

Table 2. Demographic characteristics of included studies.

Study ID, GRADE	Study region	Study period	Interpretation of COX-2	Total cohort	Age	FIGO stage
Lee 2011 ⊕⊕⊕	South Korea	January 1991 to December 2008	Negative expression = the intensity was absent to weak (+) to < 5%.	30	≤ 50 years old = 16 > 50 years old = 14	I-II = 20 III-IV = 10
Raspollini 2005 ⊕⊕⊕⊕	Italy	January 1980 to December 1999	Negative expression = the intensity was absent to weak (+) to < 10%.	24	< 60 years old = 4 ≥ 60 years old = 20	I-II = 18 III-IV = 6
Menczer 2010 ⊕⊕⊕	Israel	January 1995 to August 2008	Negative expression = the intensity was absent to weak (+) to < 10%.	27	66.8 ± 10.9 years old	I = 12 II-IV = 15
Cimbaluk 2007 ⊕⊕⊕⊕	USA	January 1985 to December 2005	Negative expression = the intensity was absent to weak (+) to < 10%.	30	65.9 (38 – 83) years old	n/r
Matsumoto 2001 ⊕⊕⊕⊕	Japan	January 1995 to December 1999	Negative expression = the intensity was absent to weak (+) to < 5%.	25	55.8 ± 7.9 years old	n/r
Hasegawa 2004 ⊕⊕⊕⊕	Japan	January 1987 to December 1996	Negative expression = the intensity was absent to weak (+) to < 5%.	49	n/r	n/r

Table 2 summarizes six studies evaluating COX-2 expression in uterine leiomyosarcoma, spanning regions including South Korea, Italy, Israel, the USA, and Japan, with study periods ranging from 1980 to 2008. COX-2 negative expression was consistently defined as absent or weak staining with thresholds varying between <5% and <10%. The total cohort across studies was 185 patients, with sample sizes ranging from 24 to 49. Age distribution varied, with mean ages reported in some studies (e.g., 66.8 ± 10.9 years in Menczer 2010 and 55.8 ± 7.9 years in Matsumoto 2001) and categorical age groups in others (e.g., ≤50 vs. >50 years in Lee 2011).[12,14,17] FIGO staging was reported in a diverse fashion, with most studies focusing on early (I-II) and advanced (III-IV) stages, though two studies did not provide staging data.

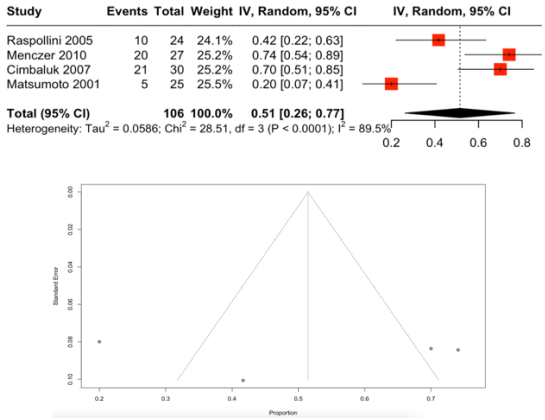

Figure 2. Meta-analysis showing the correlation between COX-2 and the total cases with positive epithelial components.

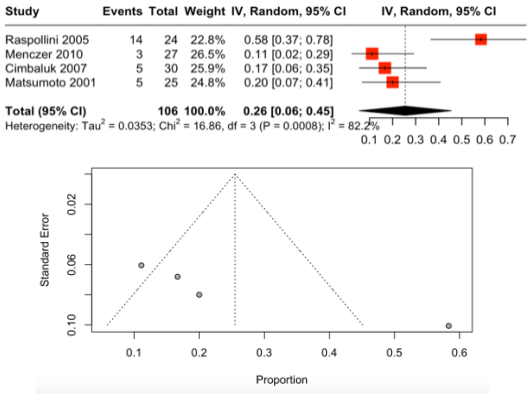

Figure 3. Meta-analysis showing the correlation between COX-2 and the total cases with positive mesenchymal components.

The meta-analysis summarizes the correlation between COX-2 expression and cases with positive epithelial and mesenchymal components, revealing distinct patterns. For positive epithelial components (**Figure 2**), the overall effect estimates of 0.51 (95% CI: 0.26–0.77) indicates a moderate positive correlation, though significant heterogeneity (I^2 = 89.5%) reflects substantial variability among studies. Similarly, for positive mesenchymal components (**Figure 3**), the overall effect estimates of 0.26 (95% CI: 0.06–0.45) suggests a weaker positive correlation, with high heterogeneity (I^2 = 82.2%) further emphasizing variability across studies.

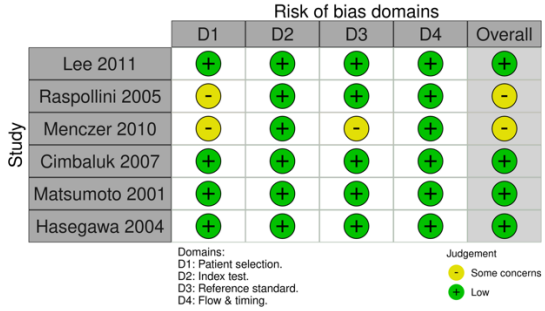

Figure 4. QUADAS-2 assessment for potential risk of bias of included studies.

The included studies demonstrated low risk of bias across QUADAS-2 domains (patient selection, index test, reference standard, flow/timing), reflecting rigorous methodological practices such as avoiding inappropriate exclusions, pre-specified thresholds, and minimized verification bias (**Figure 4**). High certainty in evidence per GRADE criteria (**Table 1**) was supported by precise, consistent effect estimates across studies, direct applicability to the research question, and absence of publication bias. These assessments underscore the reliability of the meta-analytic findings, as methodological robustness and low heterogeneity (e.g., narrow confidence intervals) reduced concerns about confounding or spurious associations. Consequently, the synthesis provides credible, generalizable conclusions on COX-2 correlations with epithelial and mesenchymal components.

Discussion

The meta-analysis assesses the association between COX-2 expression and tumor components, reporting a moderate positive correlation with epithelial components and a weak correlation with mesenchymal components. Substantial heterogeneity is identified in both analyses, with I^2 values of 89.5% for epithelial and 82.2% for mesenchymal components, attributed to differences in study designs, populations, and measurement methods. Correlation strength for epithelial components varies widely, ranging from weaker effects reported by studies such as Raspollini (2005; 0.42) and Matsumoto (2001; 0.20) to stronger associations observed in Menczer (2010; 0.74) and Cimbaluk (2007; 0.70), potentially influenced by variations in tumor subtypes or criteria for "positive" classifications.[12,14–

[16] Similarly, mesenchymal correlations show variability, with stronger effects documented by Raspollini (2005; 0.58) and weaker associations reported in Menczer (2010; 0.11) and Cimbaluk (2007; 0.17), likely reflecting inconsistencies in mesenchymal marker definitions or COX-2's limited role in stromal remodeling and epithelial-mesenchymal transition (EMT).

Biological evidence positions COX-2 as a critical mediator of inflammation and tumor progression, with its stronger association to epithelial components aligning with its established role in carcinogenesis.[18] The weaker correlation with mesenchymal components is interpreted as indicative of COX-2's limited involvement in stromal and EMT-related processes. However, the observed heterogeneity necessitates cautious interpretation of the pooled estimates, with variability in COX-2 detection methods, patient demographics, tumor stages, and study populations identified as contributing factors. Clinically, the findings support investigating COX-2 inhibitors as adjunctive therapies for epithelial-dominant cancers, while their application in mesenchymal-driven malignancies appears limited.

Mechanistic studies have consistently associated COX-2 overexpression with inflammation, angiogenesis, and epithelial cell survival, supported by preclinical and clinical evidence in colorectal, breast, and lung cancers, which aligns with the moderate correlation (0.51) observed for epithelial components.[19–21] Clinical trials have demonstrated the efficacy of COX-2 inhibitors, such as celecoxib, in reducing polyp formation in familial adenomatous polyposis (FAP) and delaying recurrence in early-stage epithelial cancers. In contrast, the weak correlation (0.26) with mesenchymal components reflects COX-2's limited involvement in EMT, a process often regulated by alternative pathways like TGF-β or Wnt.[22] This weaker association is consistent with context-dependent evidence of COX-2's role in stromal interactions, including fibroblast activation. Additionally, prior meta-analyses in epithelial cancers, such as gastric and ovarian malignancies, have reported similar pooled odds ratios (~0.4–0.6), reinforcing the reliability and consistency of COX-2's association with epithelial-driven cancers.[23,24]

Conflicting evidence surrounding COX-2 correlations underscores notable limitations and variability within the meta-analysis findings. High heterogeneity is apparent, with substantial differences in effect sizes across studies; for instance, the epithelial analysis reveals a stark contrast between Raspollini 2005 (0.42) and Menczer 2010 (0.74), likely due to methodological inconsistencies such as varying thresholds for COX-2 positivity or differences in tumor stage and subtype across populations.[14,15] Similarly, the

mesenchymal analysis shows significant divergence, with Raspollini 2005 (0.58) and Menczer 2010 (0.11) reflecting potential biases in the definitions and measurements of "mesenchymal components."[14,15] Contradictory mechanistic evidence further complicates interpretation, as some in vitro studies suggest that COX-2 may suppress mesenchymal markers like vimentin, while others report paradoxical enhancement of EMT following COX-2 inhibition in pancreatic cancer models.[25] Negative clinical trial results also question COX-2's therapeutic relevance, with large-scale studies, such as the SELECT trial, failing to demonstrate survival benefits in advanced-stage or mesenchymal-rich tumors, consistent with the weaker correlation observed for mesenchymal components.[26] Geographic and pathologic variability introduces additional complexity, as stronger COX-2 associations are more frequently reported in Asian cohorts than in Western populations, possibly due to differences in tumor biology or environmental factors.[27]

This meta-analysis has limitations, including a small study pool, potential publication bias, and the biological complexity of COX-2's role across cancer types and microenvironments. Despite these constraints, the findings suggest COX-2 expression is more strongly associated with epithelial than mesenchymal components, underscoring the need for larger, standardized studies to refine its role in tumor biology.

In terms of clinical applicability, COX-2 expression holds potential as a prognostic biomarker, aiding in stratifying ULMS patients into distinct risk groups and facilitating more personalized prognostic counseling. Additionally, COX-2 inhibitors, such as celecoxib, could be explored as adjunctive therapies for patients with high COX-2 expression, potentially enhancing treatment outcomes. These findings highlight the importance of conducting large, prospective studies to validate the prognostic significance of COX-2 and to assess the clinical efficacy of COX-2 inhibitors in the treatment of ULMS.

Conclusion

The meta-analysis identified a moderate positive correlation between COX-2 expression and cases with positive epithelial components, along with a weaker association with mesenchymal components, underscoring COX-2's preferential involvement in epithelial carcinogenesis. Despite substantial heterogeneity across studies, the findings were supported by low risk of bias and high certainty in evidence due to robust methodologies, consistent effect directions, and clinical relevance. These results indicate COX-2's potential as a therapeutic target in epithelial-dominant malignancies while highlighting its limited utility in

mesenchymal contexts. Addressing variability requires standardized protocols and stratified analyses, while future research should focus on integrating multi-omics approaches, studying larger cohorts, and conducting context-specific investigations to clarify COX-2's roles in tumor biology and resolve uncertainties from conflicting evidence.

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(Levita Dyah Kartika Suherman)

Hypoalbuminemia as a Predictor of Outcomes in Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis

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Abstract

Background : In acute myeloid leukemia (AML), hypoalbuminemia has been observed at diagnosis and during treatment, often correlating with poor clinical outcomes such as reduced remission rates, increased treatment-related toxicity, and shorter overall survival (OS). This systematic review and meta-analysis aim to investigate the prognostic value of hypoalbuminemia in patients with AML.

Methods : A comprehensive literature search was conducted across PubMed, EMBASE, and Scopus to identify relevant studies published up to January 5, 2025. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords such as “hypoalbuminemia,” “acute myeloid leukemia,” “AML,” “serum albumin,” “prognosis,” and “outcomes.” Boolean operators (AND, OR) were applied to refine the search.

Result : This systematic review and meta-analysis included 10 studies with a total sample size of 4,105 participants, of which 2,134 were male, comparing normal albumin levels to hypoalbuminemia across diverse populations. The meta-analysis comparing OS between AML patients with hypoalbuminemia and normal serum albumin levels shows a pooled HR of 1.08 (95% CI: 0.81–1.44).

Conclusions : While this meta-analysis suggests a potential association between hypoalbuminemia and poorer OS and DFS in AML patients, the lack of statistical significance and high heterogeneity caution against definitive conclusions.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal proliferation of myeloid precursors in the bone marrow, leading to impaired hematopoiesis.[1] Despite advancements in diagnostic techniques and treatment modalities, the

prognosis for AML remains poor, with five-year survival rates varying widely depending on age, comorbidities, and cytogenetic risk factors.[1,2] As a result, identifying reliable prognostic markers is critical for stratifying patients, guiding treatment decisions, and improving outcomes.

Hypoalbuminemia, defined as a serum albumin concentration below the normal range, has emerged as a potential marker of poor prognosis in various malignancies, including hematologic cancers.[3] Serum albumin plays a pivotal role in maintaining oncotic pressure, transporting hormones and drugs, and modulating inflammatory and immune responses.[3] Low albumin levels are often associated with malnutrition, systemic inflammation, and increased disease burden, factors that are known to negatively impact survival and treatment efficacy in cancer patients.

In AML, hypoalbuminemia has been observed at diagnosis and during treatment, often correlating with poor clinical outcomes such as reduced remission rates, increased treatment-related toxicity, and shorter overall survival (OS).[4,5] However, the prognostic utility of hypoalbuminemia in AML has not been systematically evaluated, and its role in clinical decision-making remains underexplored.

Given the complexity of AML and the potential for hypoalbuminemia to serve as a surrogate marker for disease severity and systemic dysfunction, a comprehensive analysis of the existing evidence is warranted. This systematic review and meta-analysis aim to investigate the prognostic value of hypoalbuminemia in patients with AML. By synthesizing data from available studies, this research seeks to evaluate the association between hypoalbuminemia and overall survival in AML patients. Understanding the prognostic implications of hypoalbuminemia in AML could provide valuable insights for risk stratification and management, ultimately contributing to improved patient care and personalized therapeutic approaches.

Material And Methods

A comprehensive literature search was conducted across PubMed, EMBASE, and Scopus to identify relevant studies published up to January 5, 2025. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords such as “hypoalbuminemia,” “acute myeloid leukemia,” “AML,” “serum albumin,” “prognosis,” and “outcomes.” Boolean operators (AND, OR) were applied to refine the search. Additionally, the reference lists of eligible studies and review articles were screened to identify further studies meeting the inclusion criteria. No restrictions were placed on language to ensure a comprehensive review. Detailed search strategy was available in **Table 1**.

Table 1. List of search terms applied across each database

Database	Search terms
PubMed	("albumin s"[All Fields] OR "albumine"[All Fields] OR "albumines"[All Fields] OR "albumins"[MeSH Terms] OR "albumins"[All Fields] OR "albumin"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields] OR ("outcome"[All Fields] OR "outcomes"[All Fields])) AND ("leukemia, myeloid, acute"[MeSH Terms] OR ("leukemia"[All Fields] AND "myeloid"[All Fields] AND "acute"[All Fields]) OR "acute myeloid leukemia"[All Fields] OR ("acute"[All Fields] AND "myeloid"[All Fields] AND "leukemia"[All Fields]))
Europe PMC	Acute myeloid leukemia AND prognosis OR outcome AND albumin
Scopus	Acute AND myeloid AND leukemia AND prognosis OR outcome AND albumin

Studies were included if they involved adult patients (≥18 years) diagnosed with acute myeloid leukemia, reported hypoalbuminemia as a baseline characteristic or its association with clinical outcomes, and provided quantitative data on outcomes such as overall survival, remission rates, or treatment-related complications. Eligible study designs included observational studies (cohort, case-control, or cross-sectional) and randomized controlled trials (RCTs) with clear methodologies. Articles were excluded if they were case reports, conference abstracts, editorials, or reviews without original data. Studies were also excluded if they lacked quantitative data on hypoalbuminemia or clinical outcomes, involved patients with other hematologic malignancies or secondary AML, or were duplicate studies with overlapping datasets.

Data extraction was performed independently by two reviewers using a standardized form, and discrepancies were resolved by discussion or consultation with a third reviewer. Extracted information included study characteristics (author, year, country, design, and sample size), patient demographics (age, sex, and baseline clinical features), the definition of hypoalbuminemia (threshold used), and clinical outcomes. The primary objective of this study was to assess the association between hypoalbuminemia and OS in AML patients. OS referred to the length of time from the start of treatment or diagnosis until death from any cause. The secondary objective was to evaluate the impact of hypoalbuminemia on disease-free survival (DFS), defined as the time from the start of treatment or diagnosis until the first occurrence of disease recurrence or relapse, or death from any cause, whichever occurred first.

The data extraction process involved gathering essential information from each study. Initially, study identification details were documented, including the study title, first author, year of publication, and journal name. Key study characteristics were extracted, such as study design (e.g., cohort, case-control, or randomized controlled trial), sample size (both total participants and those with

hypoalbuminemia), patient demographics (age range, gender, inclusion/exclusion criteria), and the study setting (e.g., hospital-based, multicenter, or country-specific). Clinical characteristics encompassed the diagnosis of acute myeloid leukemia, the definition of hypoalbuminemia (e.g., serum albumin levels), and any comorbidities present in the study population.

The quality of the included studies was assessed using the QUADAS-2 tool, which evaluates the risk of bias in diagnostic accuracy studies, considering domains such as patient selection, index test, reference standard, and flow and timing. Additionally, the certainty of the evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, which considers factors like study limitations, inconsistency, indirectness, imprecision, and publication bias to determine the overall confidence in the effect estimates. This comprehensive quality assessment ensures the reliability and robustness of the findings in this systematic review and meta-analysis.

The statistical analysis for this systematic review and meta-analysis was performed using RStudio with the meta package. A random-effects model was applied to pool the effect estimates, irrespective of heterogeneity across the studies. The log-transformed hazard ratios (HR) were used to derive the overall pooled effect estimate, with a significance threshold set at a p-value of less than 0.05. Forest plots were generated to visually present the individual study results alongside the pooled estimate, while funnel plots were created to evaluate the potential for publication bias. Bias analysis was conducted using Egger's and Begg's tests, which assess asymmetry in the funnel plot and suggest the presence of publication bias or small-study effects. The random-effects model was selected to account for variability among the studies, with statistical significance determined at a 0.05 level.

Result

The study selection process is depicted in a PRISMA flow chart (Figure 1). Initially, a total of 5,071 records were identified from three databases: PubMed (n = 116), Europe PMC (n = 4,691), and Scopus (n = 264). After removing 65 duplicate records, 5,006 records remained for screening. Out of these, 4,980 records were excluded based on the eligibility criteria. Subsequently, 26 reports were sought for retrieval, all of which were successfully retrieved. These reports were assessed for eligibility, and 16 were excluded for various reasons: 6 did not report survival analysis, 7 only reported the level of serum albumin rather than hypoalbuminemia, and 3 were meeting abstracts. Ultimately, 10 studies were included in the review.[4,6–14] (**Figure 1**).

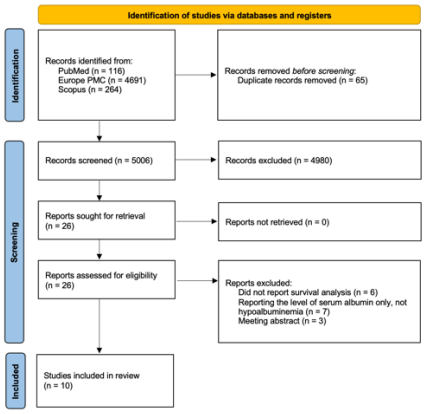

Figure 1. PRISMA flow chart illustrating the study selection process.

This systematic review and meta-analysis included 10 studies with a total sample size of 4,105 participants, of which 2,134 were male, comparing normal albumin levels to hypoalbuminemia across diverse populations. The cutoff values for hypoalbuminemia varied across studies, ranging from 2.5 to 4.0 g/dL. Detailed study demographic was available in **Table 2**.

Table 2. Demographic details of the studies included in the analysis.

Study ID, GRADE	Total cohort	Cutoff	Age	Male
Doucette 2021	715 vs 41	2.5	65.0 (18.0–91.0) vs 60.0 (18.0–85.0)	270 vs 24
⊕⊕⊕				
Wang 2019	139 vs 104	3.5	46 (14–75) vs 55 (17–80)	78 vs 55
⊕⊕⊕⊕				
Fox 2021	138 vs 75	3.5	59 vs 59.7	67 vs 38
⊕⊕⊕				
Kharfan-Dabaja 2011	141 vs 22	3	48 (19-69)	89
⊕⊕⊕⊕				
Chen 2024	299 vs 292	3.5	34 (15 - 54) vs 38 (15 - 54)	174 vs 166
⊕⊕⊕				
Sivgin 2013	60	3.2	26 (IQR 13 - 57)	42
⊕⊕⊕				
Xiao 2022	264 vs 150	3.4	60.8 ± 15.1 vs 56.2 ± 15.7	127 vs 79
⊕⊕⊕				
Murthy 2018	783	3.5	<55 years = 451 ≥55 years = 332	460
⊕⊕⊕⊕				
Artz 2016	784	3.5	50 (18 - 78)	402
⊕⊕⊕				
Yanagisawa 2022	50 vs 70	4	75 (25–88) vs 71 (45–87)	32 vs 51
⊕⊕⊕⊕				

Data presented comparing 'normal albumin levels' to 'hypoalbuminemia'

This systematic review and meta-analysis included 10 studies with a total sample size of 4,105 participants, of which 2,134 were male, comparing normal albumin levels to hypoalbuminemia across diverse populations. The cutoff values for hypoalbuminemia varied across studies, ranging from 2.5 to 4.0 g/dL. The meta-analysis comparing OS between AML patients with hypoalbuminemia and normal serum albumin levels shows a pooled HR of 1.08 (95% CI: 0.81–1.44). This suggests an 8% higher hazard of mortality in patients with hypoalbuminemia, though the confidence interval includes 1.0, indicating no statistically significant association (P = 0.61). Substantial heterogeneity was observed among the studies, with an I^2 value of 93%, suggesting variability due to differences in study characteristics or populations (**Figure 2**).

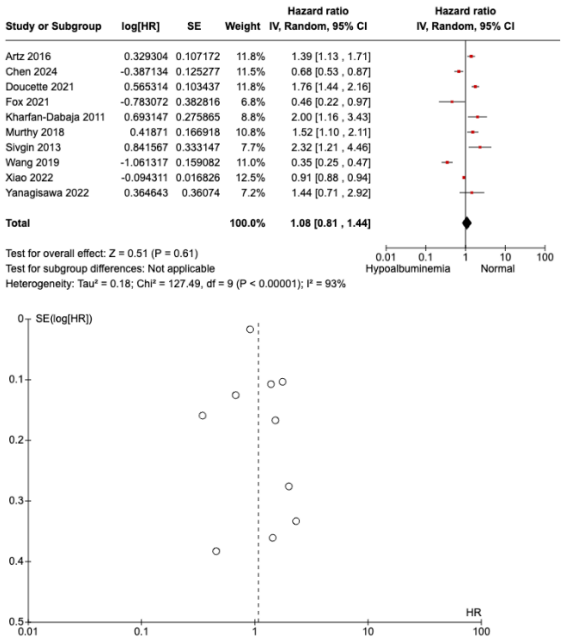

Figure 2. Meta-analysis for OS comparing between AML patients with normal serum albumin level and hypo albumin.

The meta-analysis evaluating DFS between AML patients with hypoalbuminemia and normal serum

albumin levels demonstrates a pooled HR of 1.39 (95% CI: 0.59–3.29). This result suggests a potential increase in disease recurrence or death in hypoalbuminemic patients; however, the confidence interval spans 1.0, indicating no statistically significant difference (P = 0.45). High heterogeneity was present (I^2 = 94%), reflecting significant variability across included studies (**Figure 3**).

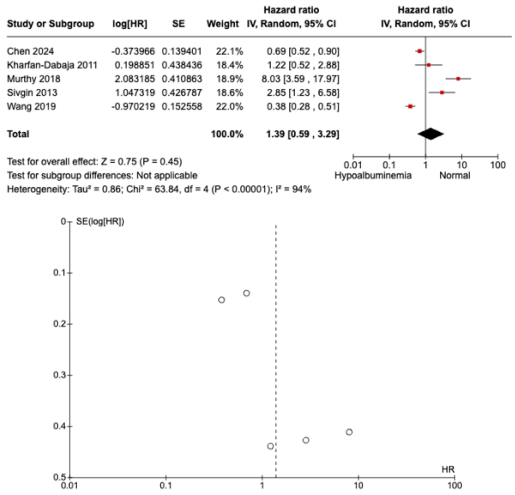

Figure 3. Meta-analysis for DFS comparing between AML patients with normal serum albumin level and hypo albumin.

In terms of bias assessment using QUADAS-2, we found that all included studies were of low to moderate risk of bias. Chen et al (2024) and Artz et al (2016) showing some concern during the bias assessment. Detailed QUADAS-2 was displayed in **figure 4**.[9,13]

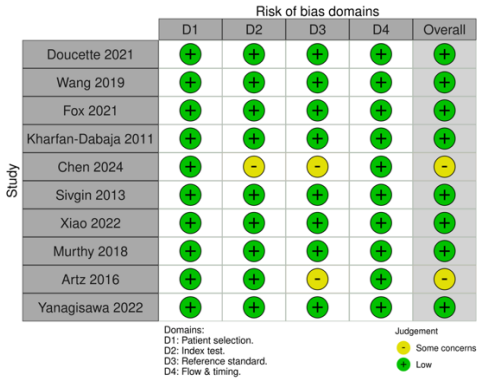

Figure 4. QUADAS-2 assessment from all eligible studies.

Discussion

This meta-analysis evaluates the prognostic significance of hypoalbuminemia in AML, given its potential as a readily measurable biomarker and modifiable risk factor. Identifying factors associated with poor outcomes in AML is essential for enhancing risk stratification and optimizing therapeutic strategies. The pooled HR for OS was 1.08 (95% CI: 0.81–1.44), indicating an 8% higher risk of mortality in patients with hypoalbuminemia compared to those with normal serum albumin levels; however, this result was not statistically significant (P = 0.61). Similarly, the pooled HR for DFS was 1.39 (95% CI: 0.59–3.29), suggesting a possible increase in disease recurrence or death among hypoalbuminemic patients, though this finding also lacked statistical significance (P = 0.45). Both analyses demonstrated substantial heterogeneity, with I^2 values of 93% for OS and 94% for

DFS, indicating considerable variability among the included studies.

Hypoalbuminemia has been associated with poor outcomes in various cancers due to its links to systemic inflammation and impaired nutritional status, both of which are critical factors in AML prognosis.[15] Albumin, as a marker of nutritional and inflammatory status, has been implicated in modulating immune responses and influencing the overall disease trajectory. Some studies included in this meta-analysis reported trends toward poorer survival outcomes in hypoalbuminemic patients, consistent with these biological hypotheses and the pooled HRs observed.

Despite these potential associations, the confidence intervals for both OS and DFS spanned 1.0, indicating no statistically significant relationship between hypoalbuminemia and survival outcomes in AML. Furthermore, several studies found no difference in survival between hypoalbuminemic and normoalbuminemic patients, suggesting the possibility that factors unrelated to albumin levels, such as treatment modalities, disease biology, or other comorbidities, may play a larger role.[16–19] These conflicting findings highlight the variability in the existing literature and the limitations of the available data.

Several limitations must be acknowledged. First, the substantial heterogeneity observed ($I^2 > 90\%$) suggests considerable variability among the included studies in terms of patient populations, definitions of hypoalbuminemia, treatment protocols, and follow-up durations. Second, the limited number of studies and small sample sizes in some cases may reduce the statistical power of the analyses, making it difficult to detect true associations. Third, confounding factors such as comorbidities, baseline disease severity, and variations in therapeutic interventions were not consistently adjusted for across studies. Lastly, the observational design of the included studies limits the ability to establish causality between hypoalbuminemia and survival outcomes.

The clinical applicability of these findings lies in the potential role of hypoalbuminemia as an easily measurable biomarker for assessing prognosis in AML patients. Although the meta-analysis did not establish a statistically significant association between hypoalbuminemia and survival outcomes, the observed trends suggest that serum albumin levels could serve as a proxy for underlying nutritional or inflammatory status, both of which influence disease progression and treatment response.[20] Monitoring albumin levels might help identify patients at higher risk who could benefit from targeted nutritional or supportive interventions to improve their overall condition and potentially enhance treatment tolerance.[21] However, given the substantial

heterogeneity and lack of definitive evidence, these findings should be interpreted cautiously, and further research is necessary before hypoalbuminemia can be routinely used in clinical decision-making for AML.

Conclusion

While this meta-analysis suggests a potential association between hypoalbuminemia and poorer OS and DFS in AML patients, the lack of statistical significance and high heterogeneity caution against definitive conclusions. Future research should focus on large-scale, well-designed studies that address confounding factors and standardize definitions of hypoalbuminemia to better evaluate its prognostic role in AML.

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(Christin Yosefin Jacobs)

The Use of Proton Pump Inhibitors in Managing Preeclampsia: A Systematic Review

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Abstract

Background: Maternal mortality remains a major global challenge, with preeclampsia (PE) as a leading cause after hemorrhage and infection. PE, a hypertensive disorder after 20 weeks of gestation, affects over. 4 million pregnancies annually, causing 50,000–70,000 maternal deaths. If untreated, it can lead to severe complications like eclampsia, HELLP syndrome, organ failure, and death. It also increases risks for the fetus, including low birth weight, preterm birth, and perinatal mortality. Early and effective management is crucial. Research suggests proton pump inhibitors (PPIs) may help by reducing sFlt-1 secretion, offering potential treatment options.

Methods: A literature search was conducted in PubMed, ScienceDirect, Directory of Open Access Journals, and Cochrane Library, yielding 354 studies. Two studies meeting inclusion and exclusion criteria were included in this review.

Result: Omeprazole and esomeprazole reduced sFlt-1 levels and increased PlGF levels in PE pregnancies, although the changes were not statistically significant. Esomeprazole increased sFlt-1 levels specifically in placental tissue. No adverse effects were reported with PPI use in the included studies.

Conclusions: PPIs (omeprazole or esomeprazole 40 mg) show potential as safe therapies for managing preeclampsia, with minimal side effects, by reducing sFlt-1 levels and increasing PlGF levels. Further research is needed to confirm these findings.

Introduction

Maternal mortality rate (MMR) is a key indicator of maternal well-being and remains a global concern. According to data from the World Health Organization (WHO), 287,000 women worldwide died during and after pregnancy, as well as during childbirth, in 2020.[1] One of the targets of the Sustainable Development Goals (SDGs) is to reduce MMR to 70 per 100,000 live births by 2030. However, in Indonesia, MMR was still at 305 per 100,000 live births in 2019. Among the leading causes of MMR, after severe hemorrhage and infections, is preeclampsia (PE). PE is a hypertensive condition occurring in pregnancies beyond 20 weeks of gestation, accompanied by organ dysfunction.[2] Annually, more than 4 million pregnant women are affected by PE,

with approximately 50,000–70,000 deaths attributed to it.[3]

Untreated PE can lead to severe complications for both mother and fetus. Maternal complications include eclampsia, hemolysis syndrome (HELLP), pulmonary edema, disseminated intravascular coagulation (DIC), kidney dysfunction, placental abruption, and even maternal death. Fetal complications include low birth weight (LBW), preterm birth, asphyxia, and perinatal death.[4] These complications pose significant risks to both maternal and fetal survival, necessitating effective therapies to manage PE and prevent eclampsia.[5]

The wide clinical variability and complexity of PE have posed challenges to fully understanding its pathogenesis and establishing appropriate therapeutic strategies. However, studies have shown that PE is caused by the placenta releasing large amounts of sFlt-1 (soluble fms-like tyrosine kinase-1) into maternal circulation. This binds to and reduces free placental growth factor (PIGF) and vascular endothelial growth factor, increasing antiangiogenic factors and triggering the release of vasoconstrictor endothelin-1 (ET-1). This, in turn, induces systemic endothelial dysfunction in the mother, leading to PE. Therefore, reducing sFlt-1 and increasing PlGF levels can restore the antiangiogenic balance in PE cases.[6,7]

Recent research has revealed that PPIs can reduce sFlt-1 release in a dose-dependent manner in placental explants or trophoblast cells. PPIs, commonly prescribed for acid reflux treatment, are considered safe for use during pregnancy.[8] This literature review analyzes the effects of PPI use in managing PE and preventing eclampsia, aiming to establish clinically relevant evidence-based medicine.

Material And Methods

The study search was conducted across various databases, including PubMed, ScienceDirect, Directory of Open Access Journals, and the Cochrane Library on 31 December 2024. The search utilized keywords such as “proton-pump inhibitor” and “preeclampsia.” Studies retrieved were filtered based on inclusion and exclusion criteria. The inclusion criteria for this review were:

- The study subjects were patients with preeclampsia or pregnant women.
- The intervention involved the administration of proton-pump inhibitors.
- The comparator included conventional therapy or placebo.
- Outcomes included levels of sFlt-1, PlGF, angiogenic factors, antiangiogenic factors, or other maternofetal factors.

The exclusion criterion was studies published more than ten years ago. Studies meeting the inclusion and exclusion criteria were accessed in full text to evaluate their availability. Articles that could not be accessed in full were excluded. Ultimately, studies meeting all criteria were included in this literature review. Study selection process was performed by all authors independently.

The search initially identified a total of 354 studies. However, only two studies fulfilled the inclusion and exclusion criteria and were subsequently analyzed in this review.

Result

Work should be reported in SI units. Undue repetition in text and tables should be avoided. Comment on validity and significance of results is appropriate but broader discussion of their implication is restricted to the next section. Subheadings that aid clarity of presentation within this and the previous section are encouraged.

The effects of PPI administration on various outcomes in preeclampsia patients can be comprehensively seen in **Table 1**.

Discussion

The Mechanism of Action of PPIs in Preeclampsia

The mechanisms by which PPIs work in preeclampsia have been extensively studied in human tissues (in vitro) and animal models (in vivo), revealing several therapeutic pathways. PPIs reduce the secretion of sFlt-1 and soluble endoglin, which are derived from trophoblasts, placental explants, and endothelial cells. They also improve endothelial function by mitigating tumor necrosis factor-induced dysfunction, inhibiting the expression of endothelial vascular cell adhesion molecule-1, reducing leukocyte adhesion to the endothelium, and preventing disruption of endothelial tube formation. Additionally, PPIs lower endothelin-1 secretion and enhance endothelial cell migration, contributing to vascular health. Notably, esomeprazole, a specific PPI, has been shown to reduce blood pressure in transgenic rat models with excessive placental expression of sFlt-1. Furthermore, PPIs exhibit antioxidant and anti-inflammatory effects by increasing endogenous antioxidant levels and reducing cytokine secretion from placental tissues and endothelial cells. These diverse mechanisms suggest that PPIs can address preeclampsia through antiangiogenic, endothelial, and anti-inflammatory pathways, offering promising therapeutic benefits.[9–11]

Effects of PPI Administration on sFlt-1 and PlGF Biomarkers in Pregnant Women with Preeclampsia

The impact of PPI administration on maternofetal biomarkers in preeclampsia has been explored in various studies.

Neuman et al. conducted a study involving 20 pregnant women diagnosed with preeclampsia between 20 and 34 weeks of gestation. Participants were over 18 years old, carrying singleton pregnancies, and diagnosed according to the International Society for the Study of Hypertension in Pregnancy 2018 criteria, which requires new-onset hypertension accompanied by proteinuria or maternal/uteroplacental dysfunction after 20 weeks of gestation. Women who had previously used PPIs, had contraindications or hypersensitivity to PPIs, or were taking medications interacting with PPIs were excluded. The participants were divided into two groups: one received 40 mg/day of omeprazole, and the other received no intervention, both observed over four days.[12]

Participants in the omeprazole group were given oral doses without specific storage conditions, instructed to take the medication in the morning before meals, and monitored for compliance. Women in the non-omeprazole group did not receive PPIs, and those experiencing acid reflux were advised to use alternative medications. Persistent reflux requiring PPIs led to their exclusion from the study.[12]

Results showed that preeclamptic women receiving omeprazole had a reduction in sFlt-1 levels compared to the non-omeprazole group, but the difference was not statistically significant (8364 vs. 13,017 pg/mL, p = 0.14). Similarly, PlGF levels were higher in the omeprazole group but not significantly so (90 vs. 55 pg/mL, p = 0.14). These findings suggest that omeprazole administration did not significantly affect sFlt-1 and PlGF levels in preeclampsia.[12]

Additionally, the study examined the effects of omeprazole and esomeprazole on placental tissue. Perfusion of the placenta with esomeprazole significantly reduced sFlt-1 levels compared to control placentas, whereas omeprazole did not show a significant effect on sFlt-1 levels.[12] Another study by Cluver et al. involved 120 pregnant women with singleton pregnancies between 26 and 31 weeks of gestation. Preeclampsia was diagnosed based on hypertension and proteinuria. Women with indications for immediate delivery, contraindications or hypersensitivity to PPIs, or those taking medications that could interact with PPIs were excluded. Participants were randomly assigned to receive either 40 mg of esomeprazole or a control treatment. The results showed that esomeprazole administration reduced sFlt-1 levels, but the difference was not statistically significant compared to the control group. Similarly, esomeprazole increased PlGF levels, but this was also not significant compared to the control group. Additionally, another preeclampsia biomarker, endothelin, showed no significant differences between the two groups.[13]

In both studies (Neuman et al. and Cluver et al.), PPI administration generally resulted in a reduction of sFlt-1 levels and an increase in PlGF levels, although the results were not statistically significant. This suggests that higher doses of PPIs (greater than 40 mg) may be necessary to achieve significant reductions in sFlt-1 and increases in PlGF levels in pregnant women with preeclampsia. The administration of esomeprazole to the placenta demonstrated a significant reduction in sFlt-1 levels, which is important as sFlt-1 plays a critical role in endothelial dysfunction in preeclampsia. A more pronounced decrease in sFlt-1 levels indicates a better therapeutic outcome in preeclampsia. Furthermore, a greater increase in PlGF levels also indicates a more favorable therapeutic outcome. Although a 40 mg dose of PPI may reduce sFlt-1 and increase PlGF, these changes are not significant at this dose.

Side Effects of PPI Use in Managing Preeclampsia

In all the included studies, the side effects of using PPIs in preeclampsia therapy, measured by circulating various maternofetal factors, did not show any adverse effects. This suggests that the use of PPIs in managing preeclampsia is relatively safe, with better effectiveness compared to control therapy with a placebo.

Table 1. The Effect of PPI Administration on Various Outcomes in Preeclampsia

Author (Year)	Population	Intervention	Outcome	Side Effects
Neuman et al. (2022)	20 pregnant women with preeclampsia (GA: 20 – 34 weeks)	Omeprazole 40mg/day vs no intervention (4 days)	No significant difference in sFlt-1, PlGF levels between the groups	No side effects reported
Cluver et al. (2018)	120 pregnant women with singleton pregnancy (GA: 26 – 31 weeks)	Esomeprazole 40mg vs placebo	No significant difference in sFlt-1, PlGF, and endothelin levels between the groups	No side effects reported

Conclusion

In this literature review, the administration of PPIs to pregnant women with preeclampsia can lower sFlt-1 levels (a factor contributing to preeclampsia) and increase PlGF levels (a protective factor for preeclampsia), but this effect was not significant at a 40mg dose. However, in placental tissue treated with the PPI omeprazole, there was a significant reduction in sFlt-1 levels. Additionally, no side effects were reported in any of the included studies. Therefore, it can be concluded that PPI therapy has the potential to address preeclampsia by lowering sFlt-1 levels and increasing PlGF levels. However, further investigation is required to determine the optimal dosage and type of PPI that can be used in pregnant women to effectively manage preeclampsia.

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(Taura Avensia)

The Association Between Smartphone Addiction, Learning Motivation Levels, and Cumulative Grade Point Average Among Students at the Faculty of Medicine, Pelita Harapan University

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Abstract

Background: Cumulative Grade Point Average (CGPA) is a crucial metric in higher education. Achieving a good CGPA increases students' opportunities for career advancement or further education. Smartphones can aid learning by boosting motivation and academic achievement but may also cause addiction when used primarily for entertainment.

Objective: To examine the relationship between smartphone addiction, learning motivation levels, and CGPA among preclinical students at the Faculty of Medicine, Pelita Harapan University.

Methodology: This cross-sectional analytical study involved 103 students with a minimum sample size of 95. Data were analyzed using SPSS version 23 through bivariate analysis.

Results: Among the respondents, 70 students were addicted to smartphone use, 94 achieved satisfactory CGPA scores, and 65 had high learning motivation. A significant relationship was found between smartphone addiction and CGPA (p = 0.029), smartphone addiction and learning motivation (p = 0.013), and learning motivation with CGPA (p = 0.000).

Conclusion: There is a significant association between smartphone addiction, learning motivation levels, and CGPA among students at the Faculty of Medicine, Pelita Harapan University.

Introduction

The cumulative grade point average (GPA) serves as a pivotal academic indicator within higher education, signifying students' proficiency and understanding of course content. Achieving a high GPA is not only critical for meeting graduation requirements but also plays a significant role in shaping career prospects and access to advanced educational pursuits.[1] As stipulated in Indonesia's Ministry of Education and Culture Regulation No. 3 of 2020 concerning Higher Education

Standards, a cumulative GPA of 3.00 or higher is deemed satisfactory, whereas a minimum GPA of 2.00 is required for the completion of an undergraduate degree.[2]

The cumulative GPA is shaped by internal factors, including intellectual capacity, attitudes towards learning, and the effectiveness of study methods employed by students,[3] as well as external factors, including the learning environment, educator quality, campus infrastructure, and parental support.[4,5] Learning motivation plays a critical role in determining students' GPA. A study conducted among nursing students at Sam Ratulangi University revealed a positive correlation between learning motivation and academic achievement, indicating that students with higher levels of motivation tend to achieve superior GPAs.[6]

Smartphones have emerged as essential academic tools, empowering students to perform a variety of educational tasks such as taking notes, creating presentations, and participating in online lectures.[7,8] When utilized effectively, smartphones can contribute to academic success. A study conducted in South Korea demonstrated that students who were proficient in smartphone-based communication tended to achieve higher GPAs.[9] However, excessive smartphone use for entertainment, such as watching videos, playing games, and social media, can lead to addiction, diminishing motivation and negatively affecting GPA.[10,11,12] Research has identified a negative correlation between smartphone addiction and GPA among adolescents. Nevertheless, the presence of contradictory findings, coupled with the 73% prevalence of moderate smartphone addiction reported among adolescents in South Tangerang, underscores the necessity for further investigation into this complex relationship.[13]

This study aims to examine the relationship between smartphone addiction, learning motivation, and GPA among preclinical students at the Faculty of Medicine, Universitas Pelita Harapan, offering insights into how smartphone addiction impacts learning motivation and academic performance.

Material And Methods

This study utilized a cross-sectional design, incorporating a categorical, unpaired comparative analytic approach to examine the relationship between smartphone addiction, learning motivation, and academic performance among students. The research was carried out over a period from August 2023 to June 2024.

The target population consisted of pre-clinical students from the 2021–2023 cohorts, who were selected through purposive sampling based on predefined inclusion criteria. These criteria included providing informed consent and meeting attendance requirements. Students who

did not provide informed consent or failed to meet the attendance criteria were excluded from the study.

Primary data were gathered using two validated instruments: the Smartphone Addiction Scale – Short Version (SAS-SV) and the motivation section of the Motivated Strategies for Learning Questionnaire (MSLQ), both of which were administered electronically. Secondary data, including attendance records and GPAs, were extracted from the university's administrative database. Data analysis was performed using Microsoft Excel 365 v2309 and SPSS 26, with the Chi-square continuity correction test applied as the primary statistical method. In cases where this test was not applicable, alternative methods such as Fisher's Exact test or Pearson's test were employed.

The questionnaires used in the study had been previously validated in scientific literature to ensure the reliability and validity of the data collected. Ethical oversight was provided by the Ethics Committee of the Faculty of Medicine at Universitas Pelita Harapan, with ethical approval granted under number 189/K-LKJ/ETIK/V/2024. Limitations of the study included the potential for response bias in questionnaire answers and the restriction of the sample to students from a single educational institution, which may limit the generalizability of the findings.

Result

Sampling was performed online using a cross-sectional questionnaire design. From a total of 110 respondents representing the 2021, 2022, and 2023 cohorts, 103 participants satisfied the inclusion criteria and did not meet any exclusion criteria. However, seven respondents were excluded for fulfilling the exclusion criteria. The diagram below illustrates the population selection process.

Table 1. Demographic Data of Study Respondents

Characteristic	n	%
Gender		
Male	31	30.10
Female	72	69.90
Cohort		
2021	35	33.98
2022	31	30.10
2023	37	35.92
Total Respondents	**103**	**100**

The distribution of respondents across cohorts revealed that the highest number of participants belonged to the 2023 cohort, with 37 individuals (35.92%). This was followed by the 2021 cohort, which comprised 35 individuals (33.98%), while the 2022 cohort had the smallest representation, with 31 individuals (30.10%).

Table 2. Respondent Characteristics Data

Characteristic	n	%
Smartphone Addiction		
Yes	70	67,96
No	33	32,04
Cumulative Achievement Index (GPA)		
Satisfactory (≥ 2.75)	94	91,26
Unsatisfactory (< 2.75)	9	8,74
Learning Motivation Level		
High	65	63,11
Medium	36	34,95
Low	2	1,94
Total Respondents	**103**	**100**

Smartphone addiction was assessed using the SAS-SV and categorized according to Arthy's distribution. The findings revealed that the majority of respondents, 70 individuals (67.96%), exhibited signs of addiction, while 33 respondents (32.04%) did not. In terms of grade point average (GPA), 94 respondents (91.26%) achieved satisfactory scores, whereas 9 respondents (8.74%) had unsatisfactory scores. Ask Explain

The learning motivation level, measured by the MSLQ and categorized according to Lisiswanti's distribution,[15] revealed that 65 respondents (63.11%) had high motivation, 36 respondents (34.95%) had medium motivation, and 2 respondents (1.94%) had low motivation.

The relationship between smartphone addiction and learning motivation was examined using the bivariate Pearson's Chi-Square test, applied to a 3x2 contingency table to determine the p-value.

Table 3. Pearson's Chi-Square Test

Variable	Learning Motivation Level			Total	*p-value*
	High	Medium	Low		
Smartphone Addiction					
Yes	50 (71,4%)	18 (25,7%)	2 (2,9%)	70	0,013
No	15 (45,5%)	18 (54,5%)	0 (0%)	33	

As shown in Table 5.3, the majority of preclinical students at the Faculty of Medicine, Universitas Pelita Harapan, exhibited smartphone addiction (70 students), with 50 of these students (71.4%) demonstrating high motivation to learn. The relationship test yielded a p-value of 0.013, indicating a statistically significant association. To further assess the strength of this relationship, an additional bivariate analysis was performed by categorizing motivation levels into two groups: "Low-Medium" and "High." The degree of association between the variables was then quantified using the Odds Ratio.

Table 4. Odds Ratio Between Smartphone Addiction and Learning Motivation

Variable	Learning Motivation Level		Total	*Odds Ratio* (95% CI)
	High	Medium-Low		
Smartphone Addiction				
Yes	50 (71,4%)	20 (28,6%)	70	3,0 (1,27 -7,085)
No	15 (45,5%)	18 (54,5%)	33	

Table 5. Fisher's Exact Chi-Square Test for GPA Values.

Cumulative GPA Variable	Satisfactory	Unsatisfactory	Total	*p-value*
Smartphone Addiction				
Yes	67 (95,7%)	3 (4,3%)	70	0,029
No	27	6	33	

Table 6. *Odds Ratio Between Smartphone Addiction and GPA*

Variable	Cumulative GPA		Total	*Odds Ratio* (95% CI)
	Satisfactory	Unsatisfactory		
Smartphone Addiction				
Yes	67 (95,7%)	3 (4,3%)	70	4,963 (1,157 – 21,288)
No	27 (81,8%)	6 (18,2%)	33	

From Table 5.4 above, it is found that the Odds Ratio value is greater than 1, which is 4.963 (95% CI = 1.157 – 21.288).

To determine the relationship between the level of learning motivation and the GPA among preclinical medical students at

Universitas Pelita Harapan, a bivariate analysis was conducted using the Chi-Square test with Pearson's Chi-Square method to obtain the p-value, as the table was in a 2x3 format.

Table 7. Pearson's Chi-Square Test

Variable	Cumulative GPA		Total	*p-value*
	Satisfactory	Unsatisfactory		
Level of Motivation				
High	64 (98,5%)	1 (1,5%)	65	
Moderate	30 (83,3%)	6 (16,7%)	36	0,000
Low	0 (0%)	2 (100%)	2	

Based on Table 5.7, the majority of preclinical students at the Faculty of Medicine, Universitas Pelita Harapan, demonstrated a high level of motivation (65 students), with 64 of these students (98.5%) achieving satisfactory GPA scores. The analysis of the relationship between learning motivation and GPA yielded a p-value of 0.000, indicating a statistically significant association.

To evaluate the strength of the relationship between motivation levels and GPA scores, additional bivariate analysis was conducted. Motivation levels were categorized into two groups: "Low-Moderate" and "High." The Odds Ratio was calculated to quantify the degree of association between these variables.

Table 8. Odds Ratio Between Learning Motivation and GPA

Variable	Cumulative GPA		Total	*Odds Ratio* (95% CI)
	Satisfactory	Unsatisfactory		
Level of Motivation				
High	64 (98,5%)	1 (1,5%)	65	17,067 (2,041 – 142,699)
Low – Medium	30 (78,9%)	8 (21,1%)	38	
Low – Medium	30 (78,9%)	8 (21,1%)	38	

Based on Table 5.8, the Odds Ratio (OR) was found to be greater than 1, specifically 17.067 (95% CI = 2.041 – 142.699). This indicates a strong association, suggesting that students with higher learning motivation are significantly more likely to achieve satisfactory GPA scores compared to those with lower motivation levels.

Discussion

The results indicate a significant relationship between smartphone addiction and learning motivation among preclinical students at the Faculty of Medicine, Universitas Pelita Harapan, with a p-value of 0.013. The OR of 3.0 (95% CI = 1.27 – 7.085) suggests that students experiencing smartphone addiction are three times more likely to exhibit high learning motivation compared to those without smartphone addiction. This finding aligns with Bagania's research, which demonstrated a positive correlation between smartphone use and learning motivation, implying that increased smartphone usage is associated with higher motivation to learn. Similarly, this is consistent with the study by Pasulu et al., which highlights that smartphone, when used as a digital learning tool, can enhance learning motivation if utilized appropriately. However, these results contrast with the findings of Sari and Lin, who reported a negative correlation between smartphone addiction and learning motivation.[13,17] The

discrepancies in the findings may be attributed to variations in smartphone usage patterns and the differing types of learning motivation demonstrated by students.

The relationship between smartphone addiction and GPA is statistically significant, with a p-value of 0.029. Students exhibiting smartphone addiction are nearly five times more likely to achieve a satisfactory GPA (OR = 4.963; 95% CI 1.157–21.288). This finding aligns with the research conducted by Han and Maria, which demonstrated that the productive use of smartphones can contribute to improved academic performance, as reflected in higher GPAs.[9,18] To maximize the academic benefits of smartphones, careful management is required.[19] Conversely, the studies by Lee and Amez found a negative correlation between smartphone addiction and academic achievement.[20,21]

Furthermore, there is a significant relationship between the level of learning motivation and GPA (p-value = 0.000). Students with high motivation are 17 times more likely to achieve a satisfactory GPA compared to those with low to moderate motivation (OR = 17.067; 95% CI 2.041–142.699). This result aligns with the findings of Eunike and Steinmeyr, who underscore the positive impact of learning motivation on academic achievement.[8,22] Learning motivation encourages individuals to study diligently and set aside distractions. Therefore, high motivation is necessary for achieving success and improving academic performance.[23] Overall, the results of this study affirm that both smartphone addiction and learning motivation significantly contribute to academic achievement, with productive smartphone use being a key factor that needs attention.

Conclusion

Based on the findings of the study conducted among preclinical students at the Faculty of Medicine, Universitas Pelita Harapan, it can be concluded that smartphone addiction demonstrates a significant association with both learning motivation and students' GPA. Furthermore, the level of learning motivation also exhibits a significant relationship with GPA. The majority of respondents were found to exhibit smartphone addiction, possess high learning motivation, and achieve satisfactory GPA scores. For future research, it is recommended to delve deeper into how students utilize smartphones within the context of learning, explore the various types of learning motivation among students, and examine additional factors—both direct and indirect—that may influence GPA. Such investigations would contribute to a more comprehensive understanding of these dynamics.

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Addressing Uncontrolled Symptoms and Communication Gaps in a Patient with Metastatic Cholangiocarcinoma: Lessons from a Palliative Care Case

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Abstract

Background : Timely integration of palliative care is essential in managing advanced cancer patients, addressing both physical symptoms and psychosocial distress. Delayed communication of prognosis and inadequate symptom control can result in unnecessary suffering for patients and emotional distress for their families.

Case Presentation : We report a 49-year-old male with metastatic cholangiocarcinoma, admitted with severe abdominal pain, nausea, and vomiting. He had undergone a Longmire procedure and gastrojejunostomy three weeks prior. Despite surgical intervention, his symptoms remained poorly controlled. Upon assessment, he expressed fear of death, while his wife struggled with the emotional burden of his prognosis, indicating a lack of prior communication regarding his terminal condition. Symptom management included oral morphine for pain and a combination of ondansetron, omeprazole, and haloperidol for nausea and vomiting, leading to improved symptom control. However, his condition deteriorated with pneumonia and respiratory failure, marking the transition to end-of-life care. He passed away peacefully 15 days after admission.

Discussion : This case highlights the consequences of delayed prognosis disclosure and inadequate early symptom management. The absence of structured communication contributed to family distress, underscoring the importance of models like SPIKES in breaking bad news. The need for a multidisciplinary palliative care approach, including psychological support and optimized opioid management, was evident.

Conclusions : Early palliative care involvement, proactive symptom control, and clear communication of prognosis are crucial in advanced cancer care. Establishing a dedicated palliative care team can improve quality of life, facilitate shared decision-making, and enhance end-of-life experiences for patients and families.

Introduction

The integration of palliative care at an early stage in the management of advanced cancer is critical for improving patient outcomes, as it ensures a comprehensive approach to symptom control, psychosocial support, and end-of-life care planning. Palliative care not only focuses on alleviating distressing physical

symptoms such as pain, nausea, and dyspnea but also addresses the emotional, psychological, and spiritual concerns of both patients and their families. Evidence suggests that early involvement of palliative care leads to better symptom management, improved quality of life, and even prolonged survival in some cases.[1,2] However, in many healthcare settings, palliative care is often introduced late in the disease trajectory, limiting its potential benefits.

Case Report

Mr R, 49 years old, presented to our emergency department with chronic unbearable abdominal pain and nausea-vomiting. His past history was significant for advanced metastatic cholangiocarcinoma diagnosed 3 months prior. Three weeks earlier, he had undergone an abdominal laparotomy with a Longmire procedure, along with a bypass gastrojejunostomy and stoma placement, in other hospital. He resided with his spouse and did not have any kids. He previously worked as an administrator in a private company but was no longer employed due to his illness. He is a devout Muslim and still regularly participates in religious activities.

During general physical examination, it was noted that Mr. R was fully alert, afebrile, with a blood pressure of 100/70 mmHg, a heart rate of 104 beats per minute, and a respiratory rate of 20 breaths per minute. He conveyed a pain intensity rating of 7 out of 10 on the numerical rating scale. He was also notable for jaundice, a functional stoma bag on the abdomen, and mild bilateral peripheral edema. Upon assessment by the digestive surgeon, the patient was referred to internal medicine and palliative care.

After clinical assessment, it was noted that the patient's primary concerns were the fear of death, and the psychological burden of his prognosis. His wife, who was not fully prepared for the severity of his condition, expressed distress and surprise upon learning of the terminal prognosis. She reported inadequate prior communication from the previous treating team regarding the grave nature of her husband's illness. Afterwards, we finalized the clinical evaluation indicating that the patient’s predominant physical problems were severe cancer pain and intractable nausea.

Easing the pain and nausea were the initial main objectives because of the preoccupation of the physical condition. Morphine 5 mg per oral (PO) QID and haloperidol 0.5 mg PO BID, as well as intravenous (IV) ondansetron 8 mg TID and IV omeprazole 40 mg BID, were prescribed for nausea-vomiting management. Pain scale was frequently monitored, and the dose of morphine was adjusted based on the evaluation.

During hospitalization, Mr. R developed acute respiratory distress, which was subsequently diagnosed as pneumonia. Despite antibiotic therapy, his

respiratory status continued to decline, leading to respiratory failure. Concomitantly, he exhibited fluctuating levels of consciousness and episodes of delirium, prompting the dying phase of his illness. Family members were counseled on the terminal nature of his condition. Mr. R's condition continued to decline, and he passed away 15 days after admission.

Discussion

The first emotional response from Mr R and his wife reflects a common psychological trajectory after breaking bad news. The patient's wife exhibited considerable emotional distress upon learning the prognosis, expressing shock and confusion. This suggests a breakdown in communication between the previous medical team and the family, where the gravity of the illness was not sufficiently conveyed. Inadequate communication about prognosis and the goals of care may lead to misunderstandings and unrealistic expectations among family members. The possibility of not delivering a straightforward prognosis due to concerns about causing emotional distress or harming the patient-doctor relationship is commonly encountered but should be avoided because clear communication is essential for patient autonomy, informed decision-making, and trust in the medical process. After several sessions of structured family meetings and clear discussions around end-of-life goals, both the patient and his wife eventually managed to accept this terminal condition.

Despite the initial outward acceptance of his wife, in the brink of her husband death, his wife did not stay beside him. This action may have been due to depression, stress reaction or other psychological reactions which should have been considered by conducting psychological/psychiatric consult for both the patient and his wife.

Cancer pain was the forefront of physical symptoms which have been addressed in the assessment of the patient. Mr. R's pain was assessed as severe based on reported numerical rating scale of 7/10; while considering his unresponsiveness to previous pain medication (NSAID), he must be managed with opioid therapy. Based on World Health Organization (WHO) analgesic ladder for management of pain, we prescribed morphine as the first-line agent for managing moderate to severe cancer pain.[3] Oral lactulose was given to prevent the constipation side effects of morphine. The patient pain was fully controlled in 30 mg total doses of oral morphine per 24 hours. In total pain assessment, we have also evaluated other aspects, including psychological, social, and spiritual factors. However, it appeared that physical pain predominates in Mr R cancer pain severity.

In addition to pain, his second predominant physical symptom was intractable nausea and vomiting. These symptoms are often multifactorial, with potential causes including bowel obstruction, opioid use, pain, and the progression of the underlying cancer. In this case, my assessment suggests that the nausea may be due to gastric irritation from NSAID use and uncontrolled cancer pain. Consequently, combination of ondansetron, omeprazole, and low-dose oral haloperidol were prescribed. These medications along with pain control successfully controlled his nausea and vomiting.

As Mr. R's condition deteriorated with the onset of pneumonia and respiratory failure, he entered the terminal phase of his illness. The transition to the dying phase necessitates us to shift our focus from active treatment to comfort care, ensuring the patient's remaining time is as peaceful and free from distress as possible. Delirium, which Mr. R developed, is also a sign of this terminal condition. After explaining this condition and the futility of further aggressive interventions to the family, additional dose of haloperidol was prescribed on top of antiemetic dose of haloperidol to ease his delirium, with continuation of the broad-spectrum antibiotics (meropenem 1 gr three times daily and levofloxacin 750 mg IV once daily) for its pneumonia. Mr. R passed peacefully after 15 days of admittance to hospital. The family bereaved peacefully and accepted the passing of Mr. R.

I believe that there was a breakdown in communication with the family at the first place. While this is not pointing blame to others, communicating the diagnosis with grave prognosis should have been taken place earlier before the last surgery. The early communication with family members regarding prognosis is essential for the effective management of anticipatory grief and the promotion of collaborative decision-making, particularly within the framework of end-of-life care.[4] Early psychological support for terminally ill patients can effectively address distress, enhancing their quality of life by helping them cope with emotional challenges and find meaning in adversity.[5] Furthermore, early integration of mental health professionals as palliative team member may facilitate effective symptom management and psychosocial support, leading to reduced rates of depression and improved emotional well-being both for the patient and his family.[6]

The physical symptoms of the patient should be comprehensively managed following the establishment of a definitive diagnosis. From the history, it seemed that both the physical symptoms of pain and nausea were not fully controlled for a great amount of time. Early referral to palliative care, ideally at the time of cancer diagnosis, is crucial for the effective management of

complex physical symptoms. The delayed consultation with palliative care, which was evident in this case, resulted in prolonged suffering for the patient, as earlier intervention could have alleviated his symptoms and improved overall wellbeing. Research indicates that the interplay between pain and emotional well-being is profound, necessitating aggressive management for controlling physical symptoms for reducing psychological distress, thus increasing comfort and quality of life for cancer patients.[7]

Clear and compassionate communication about a grave prognosis should be provided early to both the patient and their family. Unfortunately, in this case, early communication was not addressed. The SPIKES model, commonly used for delivering bad news, offers a structured approach involving six key steps: Setting, Perception, Invitation, Knowledge, Emotions, and Strategy. While this model is widely applied in palliative care, it is not well known among non-palliative care doctors in Indonesia. This gap exists because communication models like SPIKES are not typically integrated into the standard training modules for general practitioners. Encountering this case underlines the importance of disseminating this model to medical students and other clinicians, which is one of my objectives soon as both a palliative care clinician and a medical faculty staff member. By doing so, I hope to ensure clear and compassionate communication that integrates emotional support, helping clinicians manage the challenges of breaking bad news effectively.

Effective management of physical symptoms is crucial, as mitigating discomfort profoundly influences emotional health by diminishing anxiety and depression, thereby improving the overall quality of life for patients receiving palliative care.[7] Adequate cancer pain control is quintessential for enhancing the quality of life in individuals with advanced malignancies.[8] The intricate management of refractory nausea and vomiting in palliative care necessitates a comprehensive evaluation and customized treatment strategy to markedly enhance patient outcomes.

Early integration of palliative care into oncology has been shown to significantly improve outcomes for cancer patients.[1,2] This multidisciplinary approach enhances patient outcomes, with solid evidence of improved quality of life, reduced depressive symptoms alongside superior pain management and better nutritional outcomes.[2] Despite the absence of a dedicated palliative care team in our hospital's oncology unit, compelling evidence underscores the pressing necessity for its establishment. This team-based holistic approach not only addresses physical symptoms but also emphasizes emotional and spiritual well-being, offering

comprehensive support that can greatly enhance the experience of patients and their families.

Despite extensive evidence, the necessity for a dedicated palliative care team within our hospital is inadequately acknowledged, probably due to a lack of comprehensive understanding of its benefits; thus, effectively conveying this requirement to hospital management and fellow clinicians is imperative for initiating a collaborative palliative care framework. By promoting awareness and showcasing the importance of this service, we can manage to establish this care model that fulfills the physical, emotional, and psychosocial requirements of our patients.

Conclusion

The case of Mr. R underscores the importance of early palliative care integration, effective symptom management, and clear communication of prognosis. Delayed disclosure of a terminal diagnosis not only contributed to emotional distress but also hindered shared decision-making. Implementing structured communication models, such as SPIKES, in medical training can enhance patient autonomy and family preparedness. Additionally, the inadequate control of pain and nausea in this case highlights the need for early and aggressive symptom management from the time of diagnosis. Establishing a dedicated palliative care team is essential to provide comprehensive, multidisciplinary support addressing physical, psychological, and spiritual well-being. By advocating for these improvements, we can enhance the quality of end-of-life care, ensuring a more compassionate and patient-centered approach.

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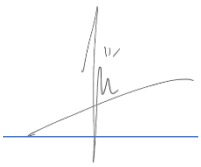

Ian Huang

Exploring Joubert Syndrome: A Rare Case Study from Indonesia

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Abstract

Background: Joubert Syndrome is a rare autosomal recessive disorder characterized by midbrain-hindbrain malformation and multisystem involvement. This study aims to present a detailed case of Joubert Syndrome from Indonesia, emphasizing clinical presentation, diagnostic challenges, and management strategies in a resource-limited setting.

Methods: This descriptive case study examines a newborn female referred for breathing difficulties and a skull tumor present since birth. Data were collected through clinical evaluations, imaging studies, laboratory tests, genetic analysis, and multidisciplinary consultations. A literature review was conducted to compare the findings with global data.

Result: The first case involved a female infant with hydrocephalus, a posterior skull mass, and microcornea. Echocardiography showed a patent foramen ovale, while genetic analysis confirmed a normal 46,XX karyotype. The second case featured a male infant with posterior meningocele, seizures, and retinal dystrophy. EEG confirmed subclinical seizures, and genetic testing identified pathogenic TMEM237 mutations consistent with Joubert Syndrome type 14. Both infants received respiratory support, antibiotics, and targeted treatments, resulting in significant clinical improvement.

Conclusions: These cases highlight the importance of multidisciplinary care and genetic testing in Joubert Syndrome diagnosis and management. Early recognition, advanced diagnostics, and consistent follow-up are crucial for optimizing outcomes, particularly in resource-limited settings.

Introduction

Joubert syndrome is a rare genetic disorder that affects a small segment of the population. Its occurrence is estimated to be between 1 in 80,000 and 1 in 10,000 individuals. Dr. Marie Joubert made the initial identification of it in 1968. Individuals with undeveloped cerebellar vermis, ataxia, aberrant eye movements, and a family history of respiratory disorders are more likely to exhibit this syndrome. Joubert syndrome frequently has an autosomal recessive mode of inheritance. Heterozygous variants in the AHI1 and OFD1 genes, on the other hand, can occasionally show dominant and X-linked inheritance, respectively.[1] This disease, which is categorized as a ciliopathy, is identified by unique brain and cerebellar abnormalities that are referred to as the "molar tooth sign," in addition to low muscle tone and delayed neurodevelopment.[2]

Joubert syndrome symptoms might include abnormal breathing patterns in neonates, such as fast breathing or periods of cessation of breathing. These symptoms usually manifest during the neonatal period. Further neurological symptoms, such as decreased muscle tone or delayed cognitive and motor skill development, may result from these patterns. Different clinical symptoms may be present with the illness, and these symptoms may be linked to problems in the kidneys, liver, or eyes. Regular supplementary testing is essential as part of proactive measures to find and treat any possible issues.[3]

Material And Methods

This descriptive case study analyzed clinical, radiological, genetic, and ophthalmologic findings in two term infants presenting with cranial anomalies and respiratory distress. Diagnostic tools included MRI, echocardiography, genetic testing, and electroencephalography (EEG).

Result

Case I

The patient was referred from another hospital due to breathing difficulties and a tumor located on the back of the skull, which had been present since birth. She weighed 2500 grams at birth and received an Apgar score of 8/9. The delivery was conducted via cesarean section. The initial diagnoses included meningoencephalocele, respiratory discomfort, potential Dandy-Walker Syndrome, and suspected hydrocephalus.

Upon examination, the patient exhibited a solid, immobile, and painless mass measuring 1.5 x 1 x 1.5 cm. On the first day, her oxygen saturation (SpO2) levels ranged from 93% to 96%, and she was breathing spontaneously while on

CPAP with settings of 7/25%. The patient demonstrated normal urine output and bowel movements and tolerated feedings well. Subsequent diagnoses included encephalocele, hydrocephalus, sepsis, dehydration, hypernatremia, and microcephaly. A comprehensive series of tests were ordered, comprising a complete blood count, CRP, sodium, potassium, calcium, blood glucose, blood gas analysis, blood culture, an anteroposterior thoracoabdominal X-ray, head ultrasound, and a consultation with neurosurgery. The treatment plan encompassed CPAP with PEEP at 7 and FiO2 at 25%, as well as administration of amoxicillin, gentamicin, and parenteral nutrition.

Table 1. Summary of the laboratory results (Case I)

	Day 1	Day 3	Day 5	Day 12	Day 17
Hb	15,8	14,9		12,7	11,2
Hct	47,3	41,1		36,5	33,2
WBC	5.230	5.52		10.120	10.610
PLT	382.000	266.000		405.000	418.000
CRP	0,2	0,0		0,9	3.1
Bilirubin Total/ Direct/ Indirect	8,7/0,14/ 8,06		2,85/0,15/2,4		0,29/0,14/ 0,15
PT/APTT	11,9/ 39,0				
Blood Glucose	74				81
Natrium/Kalium/Chloride/ Calcium	153/4,5/ 12,9/1,33			142/5,4/ 109/1,29	138/5.6/106/ 1.32
Echocardiography	Patent Foramen ovale				
Protein Total/Albumin					5.40/3.45
Ureum/Creatinine /e-GFR	16/0.4/ 173.1				
IgG/IgM TORCH	Positive (25,0) Negative (0,5)				

On the second day, the patient showed a reduction in retractions, diminished shortness of breath, and no signs of enteral intrusion. The enteral nutrition was increased to eight doses of 20 ml each via an orogastric tube, while parenteral nutrition was provided without sodium.

Antibiotics were continued. By day four, retractions were minimal, there was no tightness, although occasional desaturation was observed. The patient was then transitioned to a nasal cannula with 0.25% FiO2 at 23-25%. Full enteral nutrition was established, and antibiotics were discontinued.

An ophthalmology consultation assessed the patient, revealing the following: Corneal diameter was 9-10 mm in the right eye (OD) and 7-8 mm in the left eye (OS), with clear lenses. Fundoscopic examination showed oval papillae with clear boundaries, a cup-to-disc ratio of 0.3, and normal retinal appearance, leading to a diagnosis of microcornea in the left eye (OS < OD) and optic nerve head anomalies (OD > OS). A re-evaluation was planned in 1-2 weeks.

A genetic examination was performed using the peripheral blood culture method with G-banding, which confirmed a female karyotype (XX) with 46 chromosomes present in all 20 analyzed metaphases. No structural chromosomal abnormalities or mosaicism were detected. There were

also no mutation or microdeletion points found at the examined band resolution. Whole Exome Sequencing is highly recommended for this patient based on significant clinical findings that may indicate Joubert syndrome.

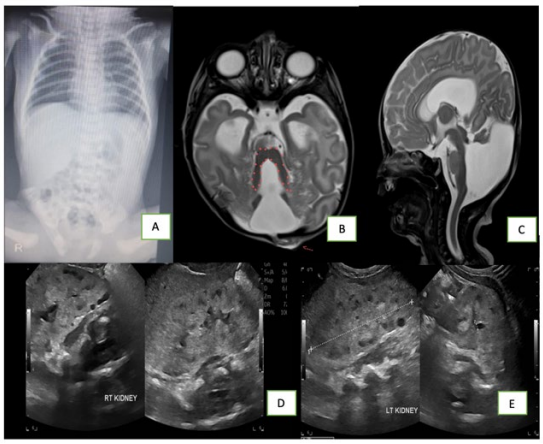

Figure 1. (A) Babygrams: No abnormalities detected in thorax and abdomen X-rays. (B) MRI axial slice showing the "molar tooth sign" (highlighted area with red dots): indicates expansion of the interpeduncular fossa and the superior cerebellar peduncles. The red arrow in the occipital region points to an atretic encephalocele. (C) MRI sagittal slice illustrating Dandy-Walker Malformation: features vermian hypoplasia with cephalad rotation and an IV ventricle associated with cystic lesions in the posterior fossa. (D)(E) Bilateral diffuse parenchymal kidney disease characterized by small, multiple cystic lesions.

Echocardiography results showed atrial situs solitus and atrioventricular and ventriculo-arterial concordance, with normal pulmonary venous drainage. The foramen ovale remained open, resulting in a left-to-right shunt. The interventricular septum was intact, with mildly dilated right atrium and right ventricle. The left aortic arch was normal, with no coarctation of the aorta (CoA) or patent ductus arteriosus (PDA). There was no pericardial effusion, and the ventricles were contracting well without paradoxical movement. It was suggested to repeat the echocardiogram at 6 to 12 months of age.

Case II

A term infant was referred for evaluation due to a lump in the cranial region. The infant was delivered via cesarean section and had previously been treated in the neonatal intensive care unit (NICU) for respiratory distress. During their NICU stay, the infant received continuous positive airway pressure (CPAP) and antibiotics. On the second day of treatment, the infant exhibited symptoms including dyspnea, rapid breathing, and seizures, which prompted additional interventions in the NICU. To ensure comprehensive care, a variety of diagnostic and management procedures were performed. The infant underwent an MRI to evaluate for a potential posterior meningocele and received appropriate treatment for pneumonia. Furthermore, a bedside Cerebral Function Monitoring (OBM) device was used to continuously monitor subclinical seizures through electroencephalography (EEG), enhancing the overall management of the infant's condition.

Table 2. Summary of Laboratory Results (Case II)

	Day 1	Day 6
Haemoglobin	12,9	13,4
Hematocrit	36,1	38,4
Leucocyte	9.740	8.370
Thrombocyte	278.000	308.000
C-reactive protein	0,0	0,3
Blood Glucose	91	
Natrium/Kalium/Chlorida/ Calcium	137/4,2/1,1/1,25	141/5,7/1,23
Ureum	18	
Creatinine	0,3	
e-GFR	221,5	

A full-term baby was born weighing 3,500 grams and is currently improving, now weighing 4,294 grams. The primary medical issue being addressed is posterior meningocele, with possible pneumonia and seizures occurring early in life. The treatment regimen includes Amoxicillin, gentamicin, and oral Keppra. An echocardiogram showed normal atrial positioning (situs solitus) and proper alignment of the atrioventricular valves and ventricles (AV-VA concordance). The foramen ovale remains patent, leading to a left-to-right shunt. The intraventricular septum is intact, and all four heart chambers are functioning normally. The heart valves are standard, and a left aortic arch is present, with no signs of aortic coarctation (CoA) or patent ductus arteriosus (PDA). The pericardium has no fluid accumulation, and the ventricles contract effectively without any paradoxical movement. A follow-up echocardiogram is scheduled for six months to evaluate the patent foramen ovale (PFO). Additionally, the patient was referred to the ophthalmology department, where they were diagnosed with coloboma, retinal dystrophy, and unequal eye movements. A medical consultation included an Otoacoustic Emission (OAE) test, which showed no abnormalities. Chromosomal analysis revealed two heterozygous pathogenic mutations in the TMEM237 gene, resulting in a genetic diagnosis of autosomal recessive Joubert syndrome type 14.

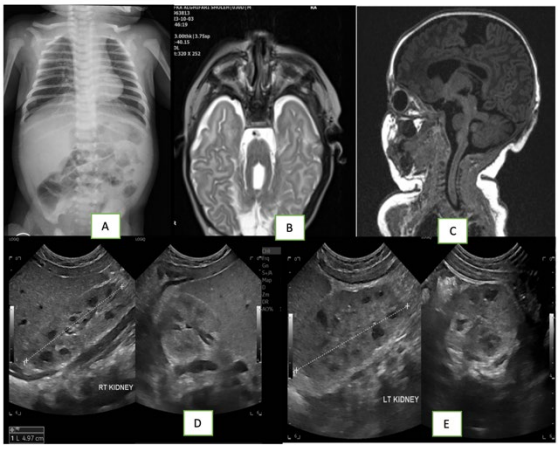

Figure 2. (A) Interstitial infiltrate in the lungs, differential diagnosis: pneumonia. (B) MRI axial slice image supporting a diagnosis of Joubert syndrome, associated with a posterior meningocele in the occipital midline (evident bone defects and the size of the lesions above), along with ventriculomegaly (ex-vacuo), anti-white matter volume loss, and hypotrophy of the corpus callosum. (C) An MRI sagittal slice showed no obvious cortical malformations, cerebral edema, encephalomalacia, bleeding, calcifications, or current intracranial lesions/masses. (D)(E) Findings suggest bilateral parenchymal kidney disease, predominantly on the left side.

Table 3. Two heterozygous pathogenic variants were identified in the TMEM237 gene, consistent with a genetic diagnosis of autosomal

Gene	Variant Coordinates	Amino Acid Change	SNP Identifier	Zygosity	In Silico Parameters*	Allele Frequences**	Type and Classification***
TMEM237	NM_001044385.3:c.550d	p.(Ser184Alafs*12)	N/A	Heterozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A Mutation Taster: N/A Conservation: Conservation_aa:	Genom AD: - ESP: - 1000 G: - CentoMD: -	Frameshift Pathogenic (class 1)
TMEM237	NM_001044385.2:c.677+1G>A	p.?	N/A	Heterozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A Mutation Taster: N/A Conservation_nt: high Conservation_aa: 2/2 likely splice effect	Genom AD: 0.0000089 ESP: - 1000 G: - CentoMD: -	Splicing Pathogenic (class 1)

Discussion

Joubert syndrome (JS) is a rare genetic disorder that is inherited in a recessive manner. It is characterized by a distinctive abnormality in the midbrain and hindbrain, known as the "molar tooth sign," along with a variety of neurological and systemic issues. The reported incidence of JS ranges from approximately 1 in 80,000 to 1 in 100,000 live births. However, recent research suggests that these prevalence rates may be higher due to improvements in diagnostic techniques and increased awareness of the condition.[4] JS is found worldwide, though its genetic composition varies significantly across different populations. Mutations linked to the development of JS have been identified in over 30 genes. Specifically, mutations causing JS to have been reported in more than 35 genes, including INPP5E, AHI1, NPHP1, NPHP6 (also known as CEP290), TMEM67 (MKS3), RPGRIP1L, ARL13B, CC2D2A, OFD1, TTC21B, KIF7, TCTN1, TCTN2, TMEM237, CEP41, TMEM138, C5orf42, TCTN3, ZNF423, TMEM231, CSPP1, and PDE6D. These mutations can lead to different phenotypic variations of the syndrome.[5]

To accurately diagnose classic Joubert Syndrome (JBTS), the following criteria must be satisfied: (a) A cranial MRI examination should reveal three specific findings: cerebellar vermis hypoplasia (CVH), a deep interpeduncular fossa, and a thickened and extended superior cerebellar peduncle; (b) There should be clear evidence of cognitive impairment or developmental delay, with varying degrees of severity; (c) Hypotonia must be present during infancy; (d) One or both of the following features, while not mandatory, can support the diagnosis: irregular breathing patterns during infancy (such as episodic apraxia and/or tachypnea, which may alternate) and abnormal eye movements (including nystagmus and/or oculomotor apraxia (OMA)).[2] Furthermore, many children diagnosed with Joubert Syndrome display distinctive facial characteristics. These may include a broad forehead, raised eyebrows, drooping eyelids, widely spaced eyes, an open jaw position, and reduced muscle

tone in the face. Some individuals with JBTS may also present with polydactyly, characterized by the presence of extra fingers and/or toes.[4]

Based on the facts presented, the first patient has multiple illnesses that may be interconnected or merit consideration as potential alternative diagnoses. The patient is demonstrating autonomous respiration using CPAP at a pressure of 7/25% and shows no signs of bradycardia or significant decreases in blood oxygen saturation. Blood oxygen (SpO2) levels have been recorded between 93-96%. The interactions between food and drink appear satisfactory, and the function of the intestines and bladder is within the expected range. However, certain health issues are evident, such as low birth weight and current birth weight, which suggest possible nutritional and developmental challenges. The potential central abnormalities are relevant to the possible occurrence of both encephalocele and hydrocephalus. Additionally, medical disorders such as sepsis, dehydration, and hypernatremia require prompt medical intervention, as they may indicate a severe medical condition that necessitates appropriate fluid administration. Although not explicitly mentioned, the potential presence of microcephaly could further complicate the patient's health. It is essential to examine the symptoms in relation to JS.[6] However, the case description does not report any characteristic signs of JS, such as ataxia or breathing difficulties. Consequently, managing these individuals requires a thorough assessment to establish an accurate diagnosis and develop an effective management strategy, which may include both medical and nutritional therapies as needed. In this case, the patient's ophthalmological assessments and chromosomal examination results did not show the typical symptoms or indicators of JS. While JS can lead to various congenital abnormalities, including ocular anomalies and structural brain defects, there were no signs of JS present in the patient's examination results. Thus, although JS should be considered a potential diagnosis when evaluating patients with eye abnormalities and neurological issues, the observed ophthalmologic findings and chromosomal analysis results do not align with the typical symptom pattern associated with JS.[7] Therefore, it is crucial to continue focusing on identifying the underlying causes of these patients' ophthalmologic observations and optic nerve irregularities, developing appropriate treatment strategies, and ensuring ongoing monitoring. This regular monitoring is vital for the patient's well-being and recovery.

The MRI results of the head revealed several significant findings. The presence of the "molar tooth sign" indicates enlargement of the interpeduncular fossa and the superior cerebellar peduncle. This

observation is commonly seen in individuals with JS, a rare genetic condition that primarily affects brain development, particularly in the brain stem. Additionally, the MRI shows features associated with Dandy-Walker Malformation (DWM), a congenital anomaly characterized by underdevelopment or abnormal formation of the posterior area of the brain (vermis cerebelli) and enlargement of the brain ventricles in the posterior region. The findings include vermian hypoplasia with cephalad rotation, meaning the cerebral vermis develops atypically and rotates towards the head.[8] Cystic lesions were identified in the posterior fossa, connected to the fourth ventricle, which could also indicate the presence of Dandy-Walker Malformation. Furthermore, an atretic encephalocele was discovered in the occipital region. This condition results from anomalies in brain development that create gaps or irregularities in the skull bones. It is important to note that the MRI findings align with the typical characteristics of Joubert Syndrome, particularly the presence of the molar tooth sign. However, Dandy-Walker Malformation and atretic encephalocele can also occur in other neurological conditions and may produce symptoms similar to those of JS. In summary, the MRI results provide general support for a potential diagnosis of Joubert Syndrome. Nevertheless, it is crucial to evaluate these findings comprehensively and consult with specialists in neurology and genetics to confirm the diagnosis accurately and develop an appropriate treatment plan for the patient.[8]

The patient was diagnosed with bilateral diffuse parenchymal kidney disease based on the abdominal ultrasound findings, which revealed numerous tiny cystic lesions. This discovery suggests multiple disorders, including multicystic dysplastic kidney (MCDK) and cystic kidney disease. Both of these conditions are inherent abnormalities of the kidneys characterized by the formation of cysts within the kidney tissue. It's important to note that cystic kidney disorders can be associated with JS, a rare genetic condition affecting brain development. Many cases of JS have been reported to exhibit renal abnormalities, such as cystic kidney disease. However, these findings alone are insufficient for confirming a diagnosis of JS, as numerous other symptoms and indicators need to be considered.[9] The absence of hydroureteronephrosis or nephrocalcinosis suggests there is no urinary tract obstruction or calcium buildup in the kidneys. Additionally, there were no abnormalities detected in the liver, gallbladder, spleen, pancreas, or intestines. The patient's medical history indicates that he was born via cesarean section (C-section) and later admitted to the Neonatal Intensive Care Unit (NICU)

due to respiratory distress. The treatment involved the use of Continuous Positive Airway Pressure (CPAP) and antibiotics. On the second day of treatment, the patient exhibited symptoms of dyspnea, rapid breathing, and convulsions, necessitating further medical intervention in the hospital. A chest X-ray revealed interstitial infiltrates in the lungs, suggesting pneumonia; however, no irregularities were observed in the abdominal region. The patient was diagnosed with several issues, including being aterm for appropriate gestational age, possible posterior meningoceles, pneumonia, and newborn seizures. He received antibacterial and anticonvulsant treatments. An echocardiogram indicated normal atrial positioning (atrial situs solitus), proper alignment of the atrioventricular valves (AV VA concordance), and the presence of a patent foramen ovale with a left-to-right shunt. While the heart appeared normal, the existence of an open foramen ovale poses a potential risk for future cardiac complications. Following this, a head MRI revealed features indicative of Joubert Syndrome, such as posterior meningoceles, ventriculomegaly, white matter atrophy, and corpus callosum hypotrophy. Despite the absence of other anomalies like cortical deformities or cerebral edema, the findings supported the diagnosis of JS. Furthermore, the ultrasound examination of the abdomen and urinary tract suggested possible bilateral parenchymal kidney disease, particularly in the left kidney, without distinct cystic characteristics or hydroureteronephrosis. Nevertheless, neither imaging technique is sufficient to definitively rule out cystic kidney disease, which may be associated with JS.

Conclusion

The diagnosis of Joubert Syndrome (JS) is supported by clinical signs and examination results, indicating potential complications such as posterior meningocele, pneumonia, and possible heart and renal abnormalities. However, confirmation requires further tests and careful monitoring of the patient's progress. Treatment and monitoring should be individualized based on the patient’s condition and the specific consequences of JS. In both cases, the male patients presented with a head lump, which aligns with Van Dorp et al. (1991), who described a case of a severely intellectually disabled boy with neurological issues, including Dandy-Walker malformation, corpus callosum hypoplasia, occipital meningoencephalocele, and bilateral coloboma of the optic nerve, along with a cystic mass behind the eyeball. Rare genetic disorders can manifest during the neonatal stage, often presenting with nonspecific symptoms that may be mistaken for common neonatal illnesses.

Tachypnea, a frequent symptom in neonates, can signal various underlying conditions, including respiratory, hemodynamic, viral, hematological, and neurological disorders. This case highlights the importance of physical examination and clinical evaluation in ensuring an accurate diagnosis and an effective treatment plan.

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(Johanes Edy Siswanto)

Multifactorial Dermatitis in an Elderly Patient with Chronic Actinic Dermatitis: A Case Report

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Abstract

Background : Chronic actinic dermatitis (CAD) is a rare, persistent photodermatosis triggered by UV and visible light, primarily affecting elderly individuals. With multifactorial etiologies, including genetic predisposition, environmental exposure, and comorbidities, CAD significantly impacts quality of life. This case report presents an elderly farmer with CAD, emphasizing the complexities of diagnosis and management in individuals exposed to high levels of sunlight due to occupational factors.

Methods : A 70-year-old male farmer presented with a two-week history of pruritus and burning sensations on his face, exacerbated by sun exposure. He had a history of seborrheic dermatitis and hypertension. Physical examination revealed erythematous, hyperpigmented plaques on sun-exposed areas, with macular erythema, erosion, and lichenification. The working diagnosis was CAD, with actinic prurigo and cutaneous T-cell lymphoma as differentials. Management included methylprednisolone, cetirizine, and a compounded cream containing clobetasol propionate and gentamicin. Preventive measures, such as the use of moisturizers, sunblock, and UV avoidance, were also emphasized. The prognosis was favorable for life and function but uncertain for complete remission due to CAD's chronic nature.

Conclusions : This case underscores the importance of an integrated approach combining pharmacological treatment and preventive strategies to manage CAD effectively. Tailored interventions addressing occupational and environmental risk factors are vital. Diagnostic limitations highlight the necessity for follow-up and the development of enhanced diagnostic tools. CAD management requires multidisciplinary collaboration to optimize patient outcomes.

Introduction

Chronic actinic dermatitis (CAD) is a rare and persistent inflammatory skin condition characterized by an abnormal sensitivity to ultraviolet (UV) and visible light, often manifesting as eczematous lesions in sun-exposed areas.1 It is most frequently observed in elderly individuals and is associated with significant morbidity, impacting their quality of life. Multifactorial in nature, CAD may result from a complex interplay of genetic predisposition, environmental exposure, and underlying comorbidities such as seborrheic dermatitis or other photosensitive disorders.[2]

In agricultural populations, such as farmers, chronic exposure to sunlight is a

critical contributing factor to the development and exacerbation of CAD.[3] The condition can present diagnostic challenges due to overlapping features with other dermatological disorders, including actinic prurigo and cutaneous T-cell lymphoma, necessitating careful clinical evaluation and differentiation.[2]

This case report discusses an elderly male farmer presenting with multifactorial dermatitis primarily manifesting as chronic actinic dermatitis. The report highlights the clinical presentation, diagnostic approach, and comprehensive management, including pharmacological and non-pharmacological strategies, while addressing the patient's unique environmental and occupational risk factors. The aim is to provide insights into the complexities of managing CAD in elderly patients with multifactorial dermatological conditions.

Case Description

Mr. E, a 70-year-old male born on October 5, 1952, worked as a farm laborer and resided in Pakancilan. He was a Muslim of Sundanese ethnicity and was married. The patient presented to the dermatology and venereology clinic with a chief complaint of itching and a burning sensation on his face that had persisted for two weeks. The symptoms initially appeared on the nape of his neck and subsequently spread to his face and arms. The itching reportedly worsened with sun exposure.

The patient had a history of seborrheic dermatitis, which was previously treated at the dermatology clinic of RSUD Ciawi with improvement. He also had a history of hypertension and had been treated at the emergency department of RSUD Ciawi for headaches accompanied by itching and peeling skin. No similar complaints were reported among his family members. The patient mentioned that he had received medication from a general practitioner in the past but was unaware of the specific medications prescribed.

As a farmer, the patient frequently engaged in outdoor activities. His home environment was well-maintained, with daily cleaning, and he maintained good social relationships with both his family and neighbors. On physical examination, he appeared moderately ill. His consciousness level was compos mentis with a Glasgow Coma Scale (GCS) score of 15 (E4M6V5). He had an elevated blood pressure of 160/100 mmHg, a heart rate of 90 beats per minute, regular and adequately filled, a respiratory rate of 20 breaths per minute, and a body temperature of 36.6°C.

The skin examination revealed multiple lesions localized to the face and left elbow, distributed regionally. The lesions were irregular in shape, erythematous, and hyperpigmented. They appeared as plaques with undefined borders and a dry surface. The primary efflorescence

observed was macular erythema, while secondary changes included erosion and lichenification.

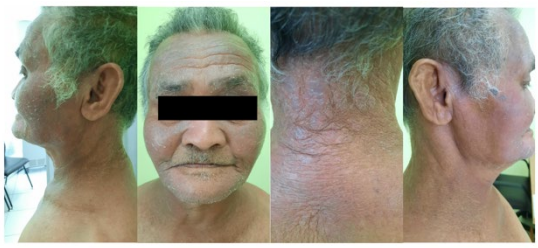

Figure 1. Physical examination of the face.

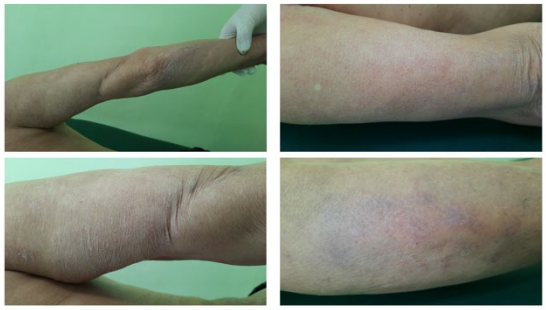

Figure 2. Physical examination of the extremity.

The working diagnosis for this patient was chronic actinic dermatitis. Differential diagnoses considered included actinic prurigo and cutaneous T-cell lymphoma. Treatment was initiated, including methylprednisolone (2x8 mg), cetirizine (10 mg), and a compounded cream containing clobetasol propionate and gentamicin. Non-pharmacological interventions included educating the patient about his condition, advising the use of moisturizers after bathing, and providing guidance on the correct use of medications. The patient was also advised to avoid scratching, maintain good hygiene, and minimize exposure to sunlight by using sunblock.

The patient's clinical condition was scheduled for monitoring to evaluate symptomatic improvement. The prognosis was considered good for life (ad vitam) and function (ad functionam), but uncertain to poor for complete recovery (ad sanationam).

Discussion

Chronic actinic dermatitis (CAD) is a chronic immune-mediated photodermatosis, predominantly affecting males aged 50 to 60, with an estimated prevalence of 0.5–2% in dermatology referrals. It arises from abnormal photosensitivity to UV light, predominantly UVB, with occasional sensitivity to UVA and visible light.[2] The pathogenesis involves an immunologically mediated reaction, resulting in eczematous inflammation on sun-exposed areas, such as the face, neck, and forearms, sparing skin folds and creases. Clinically, CAD presents as pruritic, lichenified plaques with erythema and hyperpigmentation, resembling chronic eczema, significantly impairing quality of life.[4] Diagnosis relies on phototesting to assess photosensitivity and patch testing to exclude contact allergies.[5] Management emphasizes strict photoprotection, with topical corticosteroids and emollients serving as primary therapies, while refractory cases may require systemic immunosuppressants like corticosteroids,

azathioprine, or cyclosporin. Emerging therapies, including mycophenolate mofetil (MMF), have demonstrated efficacy in improving symptoms without major adverse effects. CAD's impact extends beyond physical symptoms; persistent pruritus often disrupts daily functioning and psychological well-being.[5]

Strengths and limitations in the approach to the case

The management of the patient's condition demonstrated several strengths, including a meticulous clinical evaluation and an extensive history-taking process. By incorporating the patient's occupational, lifestyle, and environmental factors, an accurate working diagnosis of chronic actinic dermatitis was established. The treatment strategy was comprehensive, integrating both pharmacological interventions—such as anti-inflammatory agents, antipruritic medications, and infection control—and non-pharmacological measures, emphasizing lifestyle adjustments and preventive education, particularly regarding photoprotection and the use of sunblock.

Nonetheless, notable limitations were present. The absence of confirmatory diagnostic tools, such as photopatch testing or histopathological examination, restricted the precision of the diagnosis and the ability to definitively exclude alternative conditions like cutaneous T-cell lymphoma.[6] Furthermore, the absence of extended follow-up data limited the assessment of therapeutic efficacy and the potential for sustained remission. The patient's limited knowledge of prior treatments also hindered a comprehensive understanding of previous management and potential medication-related sensitivities.[7]

Discussion of the relevant medical literature

Chronic actinic dermatitis (CAD) is a complex photodermatosis triggered by hypersensitivity to ultraviolet (UV) light, commonly seen in older individuals with extensive UV exposure, particularly in outdoor occupations such as farming. The characteristic manifestations of CAD—erythematous, lichenified plaques predominantly on UV-exposed areas—closely aligned with the clinical presentation in this case.[8] The literature underscores the critical role of cumulative UV exposure and individual predispositions in the etiopathogenesis of CAD.

Evidence-based management of CAD encompasses the use of potent topical corticosteroids, systemic antihistamines, and stringent photoprotection protocols. The therapeutic regimen employed, which included methylprednisolone and clobetasol propionate cream, reflects standard clinical practice for mitigating inflammation and immune-mediated skin responses.[9] Adjunctive non-pharmacological measures, such as

emollients and rigorous avoidance of sun exposure, are pivotal for sustainable disease control. Patient adherence to photoprotective strategies, as supported by studies, is a key determinant of long-term outcomes.[10–12]

Differential diagnoses, including actinic prurigo and cutaneous T-cell lymphoma, were judiciously considered. Actinic prurigo, which often presents with similar clinical features, typically exhibits a familial predisposition and requires distinct therapeutic strategies.[13] Conversely, cutaneous T-cell lymphoma, although rare, necessitates histological confirmation due to its overlapping clinical presentation with CAD.

The rationale for the conclusions

The diagnosis of chronic actinic dermatitis was substantiated by the patient's clinical presentation, occupational background, and favorable response to initial therapy. The use of systemic corticosteroids and antihistamines effectively addressed inflammation and pruritus, while topical clobetasol propionate provided targeted treatment for localized lesions.[14] Gentamicin served to mitigate the risk of secondary bacterial infections.[15] Preventive education on UV avoidance and the application of sunblock fortified the overall management plan.[16]

The prognosis was assessed as favorable for life and functionality due to the absence of systemic involvement and the efficacy of initial symptom management. However, the uncertain prognosis for complete remission underscores the chronic, recurrent nature of CAD, which is heavily influenced by ongoing UV exposure and patient adherence to preventive measures.[2,13]

The primary "take-away" lessons

This case highlights the necessity of a multidisciplinary approach in the management of chronic actinic dermatitis, particularly in elderly patients with significant UV exposure. A comprehensive patient history and educational intervention are as crucial as pharmacological management in achieving disease control. Photoprotection remains a cornerstone of therapy, underscoring the importance of preventive strategies in mitigating disease progression and enhancing the patient's quality of life. Diagnostic limitations emphasize the need for ongoing follow-up to evaluate treatment efficacy and manage recurrent disease effectively.

Conclusion

This case report highlights chronic actinic dermatitis as a multifactorial condition requiring a multidisciplinary approach. The integration of patient history, thorough clinical examination, and targeted treatment resulted in symptomatic improvement and effective disease control.

The findings emphasize the importance of photoprotection, preventive education, and tailored pharmacological therapy in managing chronic photodermatoses, particularly in occupational settings with high UV exposure. Future research should prioritize the development of diagnostic tools and long-term follow-up strategies to enhance patient outcomes and establish standardized care protocols.

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(Hendry Purnomo Sunardi)

The Palliative Role of Colchicine on Advanced Hilar Cholangiocarcinoma Patient with Socio-Economic Challenges: A Case Report

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Abstract

Cholangiocarcinoma is a rare, slow-growing tumor that commonly presents beyond the point of resectability. Current guidelines recommend chemotherapy and radiotherapy for inoperable cases. However, palliative resources are not always accessible for patients with socio-economic barriers. Meanwhile, colchicine is a cost-effective drug and possesses anticancer effects. Here, we present a 53-year-old man with a 6-month history of painless jaundice, severe pruritus, recurrent fever, progressively growing abdominal mass, loss of appetite, and significant weight loss. He was incapable to perform adequate self-care and remained bedridden. Courvoisier sign was noted. Liver function tests show hyperbilirubinemia with elevated CA 19-9 level. Abdominal MRI 3T and MRCP showed hilar cholangiocarcinoma and obliteration of the hepatic vein. The patient and his family did not have health insurance and lived on a minimum income. Considered inoperable, the patient received daily colchicine 1 mg. Within four months, his symptoms have subsided, and he could perform several house chores. Bilirubin also showed a decreasing trend. In neoplastic cells, colchicine inhibits cell mitosis by perturbing tubulin formation. Being widely available, colchicine can be a palliative drug for terminally ill patients with socio-economic challenges. Although it improves patient performance status, we recommend further studies and close monitoring for the use of colchicine in advanced cholangiocarcinoma cases.

Introduction

Half of cholangiocarcinoma cases are inoperable and thereby receive palliative care. Current treatment recommendations for inoperable cases, including chemotherapy and radiotherapy, are shown to produce poor results.[1] Despite the advancement of research for palliative drugs, advanced cholangiocarcinoma patients often face social barriers to access these resources, leaving them with pain, discomfort, risk of developing cholangitis, and poor quality of life.[2] Meanwhile, colchicine, a cost-effective and widely

available anti-inflammatory drug for gout arthritis, was proven to have cytotoxic effects on cholangiocarcinoma cells.[3] Here, we present a case of a 53-year old man with advanced extrahepatic cholangiocarcinoma who received colchicine in his supportive care regimen.

Case Illustration

A 53-year-old man presented with a 6-month history of painless jaundice, severe pruritus, recurrent fever, progressively growing abdominal mass at the right upper quadrant, loss of appetite, and significant weight loss. In the last 3 months, he experienced recurrent hospital admissions due to melena. He had not been able to perform self-care or other activities at home and almost remained bedridden. No other remarkable medical history except for excessive alcohol intake. On physical examination, he appeared to be alert and had icteric skin. Courvoisier sign, Terry's nail, and muscle atrophy were noted. The hematology panel shows normocytic normochromic anemia. Liver function test results were as follows: total bilirubin 27,31 mg/dL, direct bilirubin 26,24 mg/dL, ALP 1035 U/L, Gamma-GT 751 U/L, AST 124 U/L, ALT 164 U/L, CA 19-9 182 U/mL. Tests for autoimmune profile, hepatitis B and C were negative. Abdominal MRI 3T and MRCP showed hilar cholangiocarcinoma measuring around 3,3 x 4,8 x 1,7 cm at the fundus of the gallbladder and 3,9 x 3,35 x 2,4 cm at the biliary bifurcation, extending towards proximal common bile duct and obliterated the portal vein. (Figure 1) Lymph nodes and other organs were within normal limits. The patient was referred to the digestive surgery department, and his condition was decided as an inoperable case.

The patient and his family were informed that he would undergo palliative care. While discussing the patient's further treatment plan, the family informed that they were not covered by the national health insurance and were living on minimum income. With limited palliative drugs in our hospital, he was given daily colchicine 1 mg, ursodeoxycholic acid 500 mg od, dexamethasone 0,5 mg tid, and curcumin 20 mg tid. He was assessed for his initial functional capacity before receiving further care with Functional Assessment Cancer Therapy – Hepatobiliary (FACT-Hep) questionnaires and received a total score of 91.

Four months later, his jaundice and cancer-related symptoms have subsided. At the same time, he was finally able to perform self-care and several house chores. Total bilirubin decreased to 1,01 mg/dL and direct bilirubin 0,91 mg/dL. His condition was assessed again with FACT-Hep questionnaires and received a total score of 140.

Discussion

Biliary tract cancers are rare, slow-growing tumors comprised of less than 1% of all malignancy cases with a male-to-female ratio of 1.5:1.[4] Most cases are difficult to diagnose and are found in the advanced disease stage. Consequently, many patients can experience many delays in receiving early and adequate care.[5]

Cholangiocarcinomas are classified according to the origin of the tumor, whether from the biliary structure within the liver, referred to as intrahepatic cholangiocarcinoma, or outside the liver parenchyma, known as extrahepatic cholangiocarcinoma. Sixty to 70% of cases of extrahepatic cholangiocarcinoma arise from hilar structure, also known as Klatskin tumor.[1] Several risk factors are related to hilar cholangiocarcinoma, including advanced age, male gender, obesity, history of primary sclerosing cholangitis, cholelithiasis, parasitic infection, and alcohol intake.[6]

Clinical manifestation depends on tumor location. Patients with intrahepatic cholangiocarcinoma are initially asymptomatic and are often incidentally found during regular checkups.[1] Extrahepatic cholangiocarcinoma cases commonly present with signs and symptoms of the obstructive biliary tract, including painless jaundice, pruritus, dark urine, and pale stools.[7] Weight loss usually indicates advanced, unresectable disease.[6] Hyperbilirubinemia usually occurs, accompanied by increased levels of alkaline phosphatase and gamma-glutamyl transferase in the state of cholestasis.[8] CA 19-9 is elevated in cholangiocarcinoma cases; however, it cannot be used for diagnostic purposes due to low sensitivity and specificity values.[9]

Diagnosing cholangiocarcinoma is best accompanied by imaging studies. Abdominal ultrasonography is handy to evaluate the local extend of disease and vascular involvement. However, the visualization result is operable-dependent. Assessment of liver parenchyma, lymph node involvement, and distant metastases would require other modalities such as computer tomography. Optimal visualization can be seen through magnetic resonance imaging in conjunction with magnetic resonance cholangiopancreatography to evaluate disease extension as it is non-invasive and highly accurate.[9]

Here, we present a case that matches the common description of an extrahepatic cholangiocarcinoma patient – a male patient that came with prolonged, obstructive jaundice and a history of excessive alcohol intake as a possible risk factor. Liver function panels showed hyperbilirubinemia, cholestatic state, and a high level of tumor marker (CA 19-9). Clinical presentation and laboratory workup were supported by the MRCP visualization of obstruction due to hilar cholangiocarcinoma at the fundus of the

gallbladder, biliary bifurcation, and proximal common bile duct with obliteration of the hepatic portal vein.

Surgery is the only curative treatment for cholangiocarcinoma, yet most cases present at an unresectable state.[10,11] Criteria for unresectable non-metastatic cholangiocarcinoma includes any of the following criteria: the patient is medically intolerant towards major operation, tumor extension to bilateral second-order biliary radicles, occlusion of the main portal vein, hepatic lobe atrophy with contralateral portal vein encasement or contralateral tumor extension to second-order biliary radicles, and proven metastases to lymph nodes, lung, liver, or peritoneum.[12,13]

This patient was not fit for surgery. Since he had difficulties in performing self-care and remained bedridden most of the time (ECOG Performance Status 3-4), he carried a higher risk of surgical complications. Furthermore, MRI/MRCP result showed the obliteration of the main portal vein, which limits the likelihood of vascular reconstruction.

Patients with unresectable cholangiocarcinoma are recommended to receive either palliative chemotherapy or radiotherapy.[10] Acknowledging his poor performance status and limited palliative modalities in our hospital, he did not have access to the recommended supportive care. The patient was the family's main source of income during his previously healthy state and retired early when he experienced these symptoms. Hence, cost also becomes the main consideration for his medical care, including drugs, diagnostic work-ups, and the number of travels to the referral healthcare facility. He received colchicine 1 mg daily as an alternative, cost-effective, yet off-label supportive drug.

Colchicine is a natural alkaloid from plants called *Gloriosa superba*.[3] The highly available drug disrupts microtubule formation and cell mitotic process in a poorly reversible manner. Since neoplastic cells are recognized to have an abnormally increased rate of mitosis, colchicine has the potential to slow disease progression. The cytotoxic effects were studied in mice that carried cholangiocarcinoma. Cellular proliferation was significantly inhibited in a dose-dependent manner. Downregulation of proliferative genes, HSD11B2 and MT-COI, was observed. Lower levels of these genes impair cellular metabolism and thereby induces cell apoptosis. Tumor growth rates were also significantly lower, resulting in smaller tumor mass after 14 days of treatment compared with the control group.[14] Other proposed anticancer effects of colchicine include inhibition of metastatic potential and angiogenesis.[15]

To assess the effect of colchicine in this case, we used the Functional Assessment of Cancer Therapy (FACT-Hep) questionnaire that includes a set of questions regarding the symptoms and quality of life in hepatobiliary cancer

patients.[16] The total score ranges from 0 – 176. The higher the score determines the better quality of life. Our patient received a score of 91 on initial presentation and 140 after 4 months of consuming colchicine. Possibly, newly diagnosed patients have uncertainties towards their future which results in a lower score. If their therapy provides a favorable clinical response, the score increases during the second assessment.[17] Since our patient experienced fewer symptoms, has improved functional capacity (ECOG Performance Status 2), and a decreasing bilirubin trend showed up, colchicine possibly contributed to providing relief from obstructive jaundice due to cholangiocarcinoma.

Although colchicine is a promising palliative drug, we are concerned about its safety profile when consumed in a long-term period. Colchicine has a narrow therapeutic window. In absence of hepatic or renal impairment, 0.6 – 1 mg of colchicine daily can benefit terminal patients.[14] To the best of our knowledge, the toxic dose of colchicine has not been established globally. However, there have been reported cases of intoxication after consuming 7 mg of colchicine per day.[18] The initial manifestation of colchicine intoxication mostly includes gastrointestinal symptoms followed by multiple organ failures and life-threatening conditions. This condition is hardly recognized as nausea and gastrointestinal upset are also common drug side effects. No antidote has ever been agreed upon if intoxication occurs. Since colchicine is rapidly distributed intracellularly, hemodialysis and plasma exchange are considered ineffective.[19]

Conclusion

While most cholangiocarcinoma cases are not surgical candidates, access to the currently recommended palliative drug is not always available. Being widely available and affordable, colchicine can provide palliative effects for patients with inoperable cholangiocarcinoma. Since colchicine is still an off-label cancer drug, we recommend further studies and close monitoring when given to terminally ill patients.

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Statement of Ethics

The subject of this case report has given his written consent to publish his case, including the publication of images.

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(Theo Audi Yanto)