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Clinical and Prognostic Value of MicroRNA-198-5p and XIAP in Sinonasal Squamous Cell Carcinoma: A Retrospective Study

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Abstract

Background: Sinonasal squamous cell carcinoma is a rare malignancy with a poor prognosis. This study explores the expression of microRNA-198 and X-linked inhibitor of apoptosis protein (XIAP), two molecules implicated in cancer progression, and analyzes their association with clinical features and survival outcomes in patients with sinonasal squamous cell carcinoma.
Materials and Methods: The outcomes of 31 sinonasal squamous cell carcinoma patients at Dr. Sardjito General Hospital, Yogyakarta, between 2017 and 2022 were retrospectively analyzed. Survival analysis was performed using Kaplan-Meier curves, and differences between survival curves were assessed using the log-rank test.
miR-198 and XIAP were both upregulated in sinonasal squamous cell carcinoma, with a positive correlation between their levels. However, their expressions showed no significant association with clinical features or survival outcomes, indicating limited prognostic value in this patient population.
Conclusions: Despite the upregulation of miR-198 and XIAP in sinonasal squamous cell carcinoma, their expression levels did not significantly impact patient survival or correlate with clinical features. These findings suggest that additional molecular factors are involved in the progression of sinonasal squamous cell carcinoma.(**International Journal of Biomedicine. 2025;15(3):490-494.**)

Keywords: microRNA-198 • XIAP • sinonasal squamous cell carcinoma • prognosis factor • expression level

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Abbreviations

HPV, human papillomavirus; **NF-κB,** nuclear factor-kappa B; **SNC,** sinonasal carcinoma; **SNSCC**, sinonasal squamous cell carcinoma; **XIAP**, X-linked inhibitor of apoptosis protein.

Introduction

The prevalence of malignant tumors in the nasal cavity and paranasal sinuses is indeed rare. Sinonasal carcinoma (SNC) represents only three to five percent of all head and neck area malignancies and 1% of all tumors. Squamous cell carcinoma is the most common subtype, followed by intestinal and non-intestinal adenocarcinoma.[1] In the Czech Republic, the incidence of SNC in 2015 was 0.69/100,000, with a mortality rate of 0.44/100,000. SNC tends to occur more frequently in older individuals and is more common in men than women.[2] Despite aggressive treatment, the overall survival rate of SNC patients remains quite poor, with only 50% of patients surviving for five years.[3]

The manifestation of SNC is linked to various risk factors, including smoking, professional exposure to cancer-causing substances, and infection with high-risk human papillomavirus (HPV).[4-6] Studies have shown that HPV-positive patients tend to have a more favorable prognosis compared to those with HPV-negative tumors.[7] Early disease

symptoms typically include rhinorrhea, epistaxis, epiphora, and nasal obstruction. However, in advanced cases, tumors can lead to symptoms such as blurred vision, diplopia, or proptosis.[8]

MicroRNAs are a group of single-stranded, non-protein-coding ribonucleic acids (RNAs) that typically range from 19 to 25 nucleotides in length. They regulate genes by binding to the three'-untranslated regions of their target genes.[9] MicroRNAs are molecules that play a significant role in the development and progression of cancer; they are believed to have tumor suppressor potential. Previous studies have shown that microRNAs are commonly downregulated in cancers such as lung cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, gastric cancer, and prostate cancer.[10-16] However, microRNA-198 (miR-198) is upregulated in retinoblastoma and squamous cell carcinoma of the tongue, suggesting that miR-198 may not always behave as a tumor suppressor in all cases. The expression profiles of miR-198 can serve as prognostic biomarkers for predicting patient survival and response to treatment.[17-19] To date, no study has investigated the expression patterns of miR-198 in sinonasal squamous cell carcinoma (SNSCC).

Another protein currently under discussion for its prognostic significance is XIAP, which stands for X-linked inhibitor of apoptosis protein. XIAP belongs to the inhibitor of apoptosis (IAP) family of proteins and plays a critical role in regulating programmed cell death, or apoptosis.[20] The XIAP protein activates nuclear factor-kappaB (NF-kB) and promotes cell survival. The anti-apoptotic nature of IAP proteins has led researchers to speculate that they might enhance cell viability, potentially promoting tumor development and resistance to anti-cancer treatments. We hypothesize that a high level of IAP proteins may be associated with the rapid progression and poor prognosis of sinonasal carcinoma.[21]

Previous studies have identified significant correlations between XIAP and miR-198 and clinical outcomes. These findings suggest that analyzing these factors could yield valuable predictive information about the response to treatment and overall survival for carcinoma patients. This study aims to investigate the prognostic significance of XIAP and miR-198 in patients with sinonasal squamous cell carcinoma.

Materials and Methods

This retrospective study examined medical records and pathological reports of individuals newly diagnosed with SNSCC who were admitted to Dr. Sardjito General Hospital in Yogyakarta, Indonesia, between 2017 and 2022. Patients with incomplete records or a prior history of cancer were excluded from the analysis. The study received approval from our institutional review board (No. KE/FK/0063/EC/2023), and written informed consent was obtained from all patients. All specimens were handled and anonymized, following ethical and legal standards.

The Quick-RNA™ Miniprep Kit was employed to isolate total RNA, including small and miRNAs, from cellular and tissue samples. The resulting RNA lacked deoxyribonucleic acid (DNA) contaminants, making it suitable for downstream applications such as Next-Gen sequencing and real-time quantitative polymerase chain reaction (RT-qPCR). Initially, the kit components, including RNA lysis buffer and deoxyribonuclease I (DNase I), were prepared by adding ethanol to the RNA wash buffer and reconstituting the lyophilized DNase I. Subsequently, samples were prepared by thawing and mixing them in the RNA lysis buffer, followed by appropriate processing of cells or tissues. The final step of total RNA purification involved the utilization of Spin-Away™ Filters and Zymo-Spin™ IIICG Columns, along with several washing steps, including DNase I treatment for the removal of DNA. The cycle threshold (CT) values were recorded, and the relative amount of miR-198 to U6 was calculated using the equation $2^{-\Delta CT}$, where $\Delta CT = (CTmiR\text{-}198 - CTU6)$.

All statistical analyses were conducted using the SPSS 29.0 software package. The significance of differences between groups was assessed using Student's t-test and the chi-square test. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. A *P*-value less than 0.05 was considered statistically significant.

Results

The study detected the expression of miR-198 and XIAP in all 31 specimens and found that both were directly proportional. However, miR-198 exhibited slightly higher expression levels than XIAP. These findings suggest that in SNSCC, both miR-198 and XIAP are upregulated (Figure 1).

Fig. 1. *miR-198 and XIAP expression from each sample.*

Correlation between miR-198 and XIAP Expression and Different Clinical Features in SNSCC

We further analyzed the association between miR-198 and XIAP expression levels and the clinical characteristics of SNSCC. SNSCC samples were classified into two groups: a low miR-198 expression group (n = 13) and a high miR-198 expression group (n = 18), and a low XIAP expression group (n = 15) and a high XIAP expression group (n = 16), based on the median miR-198 and XIAP expression levels of all SNSCC samples.

The association between clinical characteristics and the expression level of miR-198 was summarized in Table 1. We did not find any significant correlation between miR-

198 levels and clinical features in SNSCC, such as patient gender (P=0.060), age (P=0.141), tumor depth (P=0.688), and clinical stage (P=0.301). Similarly, no significant correlation was found between XIAP levels and clinical features, such as patient gender (P=0.605), age (P=0.106), tumor depth (P=0.561), and clinical stage (P=0.211).

Table 1.

Correlation between XIAP expression and different clinical features in SNSCC.

	Low XIAP expression	High XIAP expression	*P*-value
Age			
≥ 60	8	4	0.106
< 60	7	12	
Gender			
Male	8	10	0.605
Female	7	6	
Invasion depth			
T2	0	1	0.561
T3	4	3	
T4	11	12	
TNM stage			
II	0	1	0.211
III	0	2	
IV	15	13	

Table 2.

Correlation between miR-198 expression and different clinical features in SNSCC.

	Low miR-198 expression	High miR-198 expression	*P*-value
Age			
≥ 60	7	5	0.141
< 60	6	13	
Gender			
Male	5	13	0.060
Female	8	5	
Invasion depth			
T2	0	1	0.688
T3	3	4	
T4	10	13	
TNM stage			
II	0	1	0.301
III	0	2	
IV	13	15	

The relationship between miR-198 expression and several clinical characteristics in patients with SNSCC is shown in Table 2. There were no statistically significant differences between the expression of miR-198 and age (P=0.141), gender type (P=0.060), tumor invasion (P=0.688), or TNM stage (P=0.301).

Survival Analysis

The follow-up for the group of patients ranged from 4 to 215 weeks. We employed the Kaplan-Meier analysis and the log-rank test to obtain the p-value for the survival analysis. The patients were divided into categories for each miR-198 and XIAP based on their expression levels. The survival analysis results of miR-198 suggested that patients with high expression had a similar chance of survival compared to those with lower expression (P=0.363). Similarly, the survival analysis results of XIAP indicated that the chance of survival was not affected by the expression level (P=0.883).

Kaplan-Meier survival curves of 31 sinonasal squamous cell carcinoma patients based on miR-198 expression status. There is no significant difference in prognosis between patients in the low-expression group and those in the high-expression group (P=0.363, log-rank test) (Figure 2). Kaplan-Meier survival curves of 31 sinonasal squamous cell carcinoma patients based on XIAP expression status. There is no significant difference in prognosis between patients in the low-expression group and those in the high-expression group (P=0.883, log-rank test) (Figure 3).

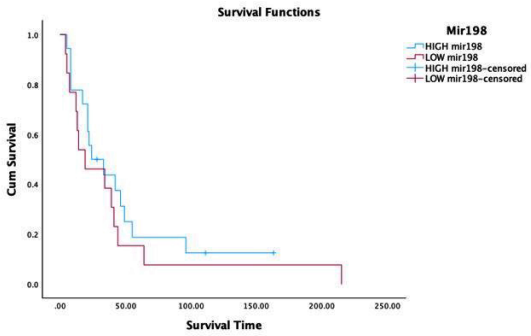

Fig.2. *Kaplan-Meier survival curves of 31 SNSCC patients based on miR-198 expression status. There is no significant difference in prognosis between patients in the low expression group and those in the high expression group (P=0.363, log-rank test).*

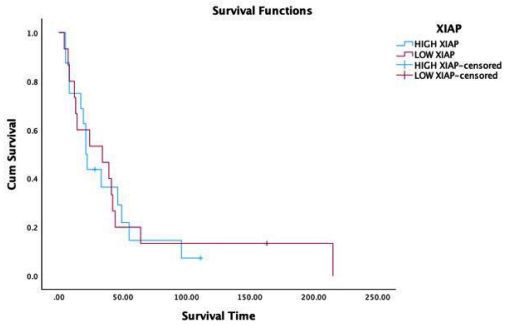

Fig.3*. Kaplan-Meier survival curves of 31 SNSCC patients based on XIAP expression status. There is no significant difference in prognosis between patients in the low expression group and those in the high expression group (P=0.883, log-rank test).*

Discussion

In the current study, we observed an upregulation of both miR-198 and XIAP in human SNSCC tissues and noted a direct correlation between their levels. However, we did not find a significant correlation between the expression levels and aggressive clinical characteristics. Furthermore, our Kaplan-Meier analysis did not reveal any notable differences between patients with low and high expression levels of these markers. To the authors' knowledge, this is the first study to analyze the expression and clinical significance of miR-198 and XIAP in SNSCC.

The observed upregulation of miR-198 and XIAP in SNSCC specimens suggests their potential roles as oncogenic drivers in SNSCC development.[17,18,20,21] Previous studies have implicated miR-198 dysregulation in various cancers, where it exerts its oncogenic effects by targeting tumor suppressor genes or modulating key signaling pathways.[15] Similarly, XIAP overexpression has been associated with resistance to apoptosis and chemotherapy in several malignancies, facilitating tumor survival and progression.[20,21] However, the lack of significant correlation between miR-198/XIAP expression and clinical features in SNSCC suggests that multiple factors are involved in the complex interplay of the carcinoma's pathogenesis.

The findings in this study indicate that the expression levels of miR-198 and XIAP do not significantly impact patient survival in SNSCC. These findings contrast other cancer types, where abnormal expression of these molecules is linked to a worse prognosis.[15,22] The heterogeneous characteristics of SNSCC and the influence of other molecular alterations on patient outcomes may explain this discrepancy. Additionally, the retrospective design and relatively small sample size of the study may limit the applicability of the results. Therefore, larger prospective studies are needed to validate these findings and provide further insight into the molecular mechanisms behind the progression of SNSCC.

This study provided new insights into the expression patterns of miR-198 and XIAP in SNSCC and their potential implications for clinical management. Although both molecules were upregulated in SNSCC, their expression levels did not significantly correlate with clinical features or patient survival. These results underscored the complexity of SNSCC biology, highlighting the need for further research to uncover the underlying molecular mechanisms driving its progression. Targeting miR-198 and XIAP signaling pathways could offer effective therapeutic strategies for treating SNSCC, necessitating further investigation in preclinical and clinical settings.

The limitation of this study is the sample size; therefore, further prospective analysis with a larger number of patients is warranted to validate these conclusions.

Ethical Considerations

This study was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, with registration number No.KE/FK/0063/EC/2023.

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Competing Interests

The authors declare that they have no competing interests.

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