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THE RELATIONSHIP BETWEEN FORKHEAD BOX M1 (FOXM1) EXPRESSION AND NASOPHARYNGEAL CARCINOMA STAGE

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ABSTRACT
Nasopharyngeal carcinoma (NPC) is a malignancy with a high incidence in Southeast Asia and is frequently diagnosed at an advanced stage. Forkhead box M1 (FOXM1) is a transcription factor involved in cell-cycle progression, proliferation, invasion, migration, and metastasis. Previous studies have reported FOXM1 overexpression in NPC and its association with tumor progression; however, its relationship with clinical stage remains unclear. To determine the association between Forkhead Box M1 (FOXM1) expression and the stage of nasopharyngeal carcinoma. This analytic observational study used a cross-sectional design and was conducted at the Otorhinolaryngology outpatient clinic of Adam Malik Hospital, Medan, from 2022 to 2024. The study population comprised patients with histopathologically confirmed nasopharyngeal carcinoma. A total of 39 patients who fulfilled the inclusion and exclusion criteria were enrolled using a non-probability consecutive sampling technique. Histopathological examination was performed at the Department of Anatomical Pathology, Adam Malik Hospital, Medan, while FOXM1 mRNA expression was assessed at the Integrated Laboratory, Faculty of Medicine, Universitas Sumatera Utara, using real-time reverse transcription polymerase chain reaction (RT-qPCR) and expressed as ΔCt values. Clinical stage was determined according to the American Joint Committee on Cancer (AJCC) 8th edition TNM classification. Data were analyzed using univariate and bivariate analyses, and the Kruskal–Wallis test was performed to assess the relationship between FOXM1 expression and clinical stage. Among the 39 patients, 28 (71.8%) were male, and the most common age group was 41–60 years (64.1%). Most patients had advanced disease, with T4 being the most frequent primary tumor category (46.2%). The mean FOXM1 ΔCt value was 7.05 ± 3.38, with a median of 6.01 and a range of −1.96 to 13.86. Median FOXM1 ΔCt values were 8.78 (4.98–12.52) in patients with stage II–III disease, 6.28 (−1.96–13.86) in stage IVA, and 5.39 (4.92–12.20) in stage IVB. Although ΔCt values decreased progressively with increasing clinical stage, indicating a trend toward higher FOXM1 expression in advanced disease, the difference was not statistically significant ($p = 0.140$). There was no statistically significant relationship between FOXM1 mRNA expression and clinical stage of nasopharyngeal carcinoma. However, the progressive decrease in ΔCt values from earlier to more advanced stages suggests a potential trend toward increased FOXM1 expression with disease progression.

Keywords: clinical stage; forkhead box M1; gene expression; nasopharyngeal carcinoma; RT-qPCR

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy originating from the epithelial lining of the nasopharynx. Although relatively rare in Western countries, NPC has a high incidence in southern China and Southeast Asia. Its development is associated with several factors, including Epstein–Barr virus (EBV) infection, environmental factors, and genetic predisposition (Wong et al., 2021). NPC is often diagnosed at an advanced stage, and regional lymph node involvement and distant metastasis contribute to poor prognosis. Current treatment includes radiotherapy, chemotherapy, and chemoradiotherapy; however, treatment outcomes may be limited by adverse effects, local recurrence, and distant metastasis. Therefore, understanding the molecular mechanisms underlying

NPC progression is important for identifying potential therapeutic targets (Shah and Nagalli, 2022; Sinha et al., 2024).

Forkhead box M1 (FOXM1) is a member of the forkhead family of transcription factors and plays an important role in cell-cycle progression, particularly the G1–S and G2–M transitions, as well as mitotic spindle integrity. FOXM1 overexpression has been associated with the development and progression of various malignancies. In addition, increased FOXM1 expression can promote epithelial–mesenchymal transition (EMT), migration, and invasion of cancer cells (Kalathil et al., 2021; Khan et al., 2023). Therefore, FOXM1 has been proposed as a potential therapeutic target in cancer.

Several studies have reported FOXM1 overexpression in NPC and demonstrated that suppression of FOXM1 reduces NPC cell proliferation and other aggressive tumor characteristics. FOXM1 may therefore contribute to NPC progression through its effects on tumor proliferation, migration, and invasion (Wang et al., 2021; Khan et al., 2023). However, the relationship between FOXM1 expression and the clinical stage of NPC remains incompletely understood (Merjaneh et al., 2024; Sher et al., 2022).

Given the potential role of FOXM1 in tumor progression and metastasis, increased FOXM1 expression may be associated with more advanced clinical stages of NPC (Yang et al., 2022). Clinical staging based on the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification provides an established framework for assessing disease extent and prognosis in nasopharyngeal carcinoma (Rueda et al., 2026). Therefore, this study aimed to determine the association between Forkhead Box M1 (FOXM1) expression and the clinical stage of nasopharyngeal carcinoma.

METHOD

This analytic observational study used a cross-sectional design. The study was conducted at the Otorhinolaryngology–Head and Neck Surgery Department of Adam Malik Hospital, Medan, Indonesia, during the 2022–2024 study period. The study population comprised patients with histopathologically confirmed nasopharyngeal carcinoma who were treated at Adam Malik Hospital. A total of 39 patients who fulfilled the inclusion and exclusion criteria were enrolled using a non-probability consecutive sampling technique.

Histopathological examination was performed at the Department of Anatomical Pathology, Adam Malik Hospital, Medan. Tumor tissue samples obtained from eligible patients were used for molecular examination. RNA was isolated from the samples, followed by complementary DNA (cDNA) synthesis. FOXM1 mRNA expression was subsequently assessed using real-time reverse transcription polymerase chain reaction (RT-qPCR) at the Integrated Laboratory, Faculty of Medicine, Universitas Sumatera Utara. The RT-qPCR assay was performed using specific forward and reverse primers for FOXM1, with SsoFast EvaGreen SuperMix as the reaction reagent. The amplification was performed using a Rotor-Gene real-time PCR system. FOXM1 expression was evaluated based on the ΔCt value, with lower ΔCt values indicating higher gene expression.

Clinical and demographic data were obtained from the medical records of the study participants. Clinical stage was determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification, including assessment of the primary tumor (T), regional lymph node involvement (N), and distant metastasis (M).

Data were analyzed using univariate and bivariate analyses. Univariate analysis was used to describe the distribution of categorical variables as frequencies and percentages, whereas numerical variables were presented as mean ± standard deviation or median and range, as appropriate.

Bivariate analysis was performed to assess the relationship between FOXM1 mRNA expression and clinical characteristics. The Kruskal–Wallis test was used to compare FOXM1 expression among clinical-stage groups. Statistical significance was set at $p < 0.05$. The study was conducted after obtaining ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia with approval number No. 2603218-KEPK-USU.

RESULT

Demographic Characteristics of the Study Subjects

The study included 39 patients with nasopharyngeal carcinoma (NPC) who were treated at the Head and Neck Surgical Oncology Subdivision, Department of Otorhinolaryngology–Head and Neck Surgery, Faculty of Medicine, Universitas Sumatera Utara/Adam Malik Hospital, Medan, during the period from 2022 to 2024. All subjects fulfilled the inclusion criteria. Table 1 presents the demographic and clinical characteristics of patients with nasopharyngeal carcinoma treated at Adam Malik Hospital, Medan. The data include the distribution of sex, age, histopathological type, primary tumor stage (T), regional lymph node stage (N), and clinical stage.

Table 1.
Demographic and Clinical Characteristics of Patients with Nasopharyngeal Carcinoma Treated at the Oncology–Head and Neck Surgery Subdivision, Department of Otorhinolaryngology–Head and Neck Surgery, Faculty of Medicine, Universitas Sumatera Utara/Adam Malik Hospital, Medan, during the 2022–2024 Period

Karakteristik Demografi dan Klinis	n = 39
Tahun, f (%)	
2022	10 (25,6)
2023	17 (43,6)
2024	12 (30,8)
Jenis Kelamin, f (%)	
Laki-Laki	28 (71,8)
Perempuan	11 (28,2)
Usia, tahun	
Rerata ± SD	49,59 ± 10,67
Median (Min – Mak)	50 (27 – 40)
20 – 40 tahun	7 (17,9)
41 – 60 tahun	25 (64,1)
> 60 tahun	7 (17,9)
Tipe Histopatologi, f (%)	
Non Keratinizing SCC	32 (82,1)
Undifferentiated Carcinoma	7 (17,9)
T, f (%)	
T1	2 (5,1)
T2	6 (15,4)
T3	13 (33,3)
T4	18 (46,2)
N, f (%)	
N0	9 (23,1)
N1	11 (28,2)
N2	9 (23,1)
N3	10 (25,6)
Metastasis, f (%)	
M0	34 (87,2)
M1	5 (12,8)
Stadium, n (%)	
II	1 (2,6)
III	10 (25,6)
IV A	23 (59)
IV B	5 (12,8)

Most patients were male (71.8%) and aged 41–60 years (64.1%), with a mean age of 49.59 ± 10.67 years. Non-keratinizing squamous cell carcinoma was the predominant histopathological type (82.1%). Regarding TNM classification, T4 was the most frequent primary tumor category (46.2%),

while N1 was the most common regional lymph node category (28.2%). Most patients had no distant metastasis (M0; 87.2%). Overall, advanced-stage disease predominated, with stage IVA being the most common (59.0%), followed by stage III (25.6%) and stage IVB (12.8%).

FOXM1 Gene Expression in Patients with Nasopharyngeal Carcinoma Treated

Table 2 summarizes the quantitative data on *FOXM1* (*Forkhead box protein M1*) gene expression obtained through real-time quantitative PCR (qPCR) analysis in 39 patients with nasopharyngeal carcinoma. The ΔCt value reflects the relative level of gene expression, with higher ΔCt values indicating lower gene expression (hypoexpression), as lower levels of the target gene require a greater number of amplification cycles to be detected.

Table 2.
FOXM1 Gene Expression in Patients with Nasopharyngeal Carcinoma Treated

ΔCT Gen FOXM-1	**n = 39**
Rerata ± SD	7,05 ± 3,38
Median (Min – Mak)	6,01 (-1,96 – 13,86)

The mean ΔCt value of FOXM1 was 7.05 ± 3.38, with a median of 6.01 and a wide range from −1.96 to 13.86, indicating substantial interindividual variability in FOXM1 expression. In qPCR analysis, lower ΔCt values indicate higher gene expression, whereas higher ΔCt values indicate lower expression. The wide ΔCt range suggests considerable heterogeneity in FOXM1 expression among patients with nasopharyngeal carcinoma.

Association Between FOXM1 Gene Expression and Histopathological Type in Patients with Nasopharyngeal Carcinoma Treated

The following Table 3 presents the analysis of the association between FOXM1 gene expression levels, expressed as Ct values, and histopathological type in patients with nasopharyngeal carcinoma treated at Adam Malik Hospital, Medan. The analysis was performed on two main histopathological groups, namely Non-Keratinizing Squamous Cell Carcinoma (SCC) and Undifferentiated Carcinoma, using an independent t-test to determine whether there was a statistically significant difference between the two groups.

Table 3.
Association Between FOXM1 Gene Expression and Histopathological Type in Patients with Nasopharyngeal Carcinoma Treated

Tipe Histopatologi	n	ΔCT Gen FOXM-1, Rerata ± SD	p
Non-Keratinizing SCC	32	6,67 ± 3,24	0,136*
Undifferentiated Ca	7	8,78 ± 3,75	

T Independen

Patients with non-keratinizing SCC (n=32) had a mean FOXM1 ΔCt value of 6.67 ± 3.24, compared with 8.78 ± 3.75 in patients with undifferentiated carcinoma (n=7). Given the inverse relationship between ΔCt values and gene expression, FOXM1 expression was numerically higher in the non-keratinizing SCC group. However, the independent t-test showed no statistically significant difference in FOXM1 expression between the two histopathological groups (p = 0.136).

Association Between FOXM1 Gene Expression and Tumor Mass Extension in Patients with Nasopharyngeal Carcinoma

Table 4 presents the distribution of FOXM1 (Forkhead box protein M1) gene expression values according to the categories of primary tumor extension (T1–T4) in 39 patients with nasopharyngeal carcinoma. This analysis aimed to evaluate whether differences in FOXM1 expression levels were observed with increasing local tumor progression, as clinically reflected by the T classification of the TNM staging system.

Table 4.
Association Between FOXM1 Gene Expression and Tumor Mass Extension in Patients with Nasopharyngeal Carcinoma

Perluasan Tumor	n	ΔCT Gen FOXM-1	p
T1	2	5,19 (4,98 – 5,39)	0,255
T2	6	7,54 (2,68 – 11,91)	
T3	13	6,92 (4,8 – 13,86)	
T4	18	5,97 (-1,96 – 12,2)	

Data are presented as median (minimum–maximum).
**Kruskal–Wallis test*

FOXM1 expression was evaluated across four primary tumor categories (T1–T4). The median ΔCt values were 5.19 (range, 4.98–5.39) for T1 (n=2), 7.54 (range, 2.68–11.91) for T2 (n=6), 6.92 (range, 4.80–13.86) for T3 (n=13), and 5.97 (range, −1.96–12.20) for T4 (n=18). Although the T4 group showed a lower median ΔCt, indicating a numerical trend toward higher FOXM1 expression, the Kruskal–Wallis test demonstrated no statistically significant difference in FOXM1 expression across T1–T4 categories (p = 0.255).

Association Between FOXM1 Gene Expression and Lymph Node Enlargement in Patients with Nasopharyngeal Carcinoma

Table 5 presents the analysis of the association between FOXM1 gene expression, represented by the ΔCt values, and the status of regional lymph node enlargement (N classification) in patients with nasopharyngeal carcinoma.

Table 5.
Association Between FOXM1 Gene Expression and Lymph Node Enlargement in Nasopharyngeal Carcinoma

KGB	n	ΔCT Gen FOXM-1	p	Posthoc		
				N1	N2	N3
N0	9	4,98 (1,67 – 10,89)	0,022*	1,000	0,014	1,000
N1	11	6,16 (-1,96 – 12,20)			0,391	1,000
N2	9	9,5 (5,63– 12,52)				0,233
N3	10	5,73 (2,68 – 13,86)				

Data are presented as median (minimum–maximum).
**Kruskal–Wallis test*

FOXM1 expression was evaluated across four regional lymph node categories (N0–N3). The median ΔCt values were 4.98 (range, 1.67–10.89) for N0 (n=9), 6.16 (range, −1.96–12.20) for N1 (n=11), 6.01 (range, −1.96–13.86) for N2 (n=9), and 5.73 (range, 2.68–13.86) for N3 (n=10). The Kruskal–Wallis test demonstrated a statistically significant difference in FOXM1 expression across the N-stage categories (p = 0.022). Post-hoc analysis showed that the significant difference was observed only between the N0 and N2 groups (p = 0.014), while no significant differences were found between N0 and N1 (p = 1.000), N0 and N3 (p = 1.000), N1 and N2 (p = 0.391), N1 and N3 (p = 1.000), or N2 and N3 (p = 0.233).

Association Between FOXM1 Gene Expression and Tumor Metastasis in Patients with Nasopharyngeal Carcinoma

Table 6 presents the analysis of the association between FOXM1 gene expression and distant metastasis status (M classification) in patients with nasopharyngeal carcinoma.

Table 6.
Association Between FOXM1 Gene Expression and Tumor Metastasis in Patients with Nasopharyngeal Carcinoma

Metastasis Tumor	n	ΔCT Gen FOXM-1	p
M0	34	6,3 (-1,96 – 13,86)	0,610
M1	5	5,39 (4,92 – 12,2)	

Data are presented as median (minimum–maximum).
**Kruskal–Wallis test*

FOXM1 expression was evaluated according to the presence or absence of distant metastasis. The median ΔCt value was 6.30 (range, −1.96–13.86) in patients without distant metastasis (M0, n=34) and 5.39 (range, 4.92–12.20) in those with distant metastasis (M1, n=5). The M1 group showed a lower median ΔCt value, indicating a numerical trend toward higher FOXM1 expression. However, the Kruskal–Wallis test demonstrated no statistically significant difference in FOXM1 expression between patients with and without distant metastasis (p = 0.610).

Association Between FOXM1 Gene Expression and Clinical Stage of Nasopharyngeal Carcinoma

Table 7 presents the analysis of the association between FOXM1 gene expression levels, expressed as Ct values, and the clinical stage of nasopharyngeal carcinoma in patients treated at Adam Malik Hospital, Medan.

Table 7.
Association Between FOXM1 Gene Expression and Clinical Stage of Nasopharyngeal Carcinoma

Stadium	n	ΔCT Gen FOXM-1	p
Stadium II dan III	11	8,78 (4,98 – 12,52)	0,140
Stadium IVA	23	6,28 (-1,96 – 13,86)	
Stadium IVB	5	5,39 (4,92 – 12,2)	

Data are presented as median (minimum–maximum).
**Kruskal–Wallis test*

FOXM1 expression was evaluated across three clinical-stage groups. The median ΔCt value was 8.78 (range, 4.98–12.52) in patients with stage II–III disease (n=10), 6.28 (range, −1.96–13.86) in those with stage IVA disease (n=23), and 5.39 (range, 4.92–12.20) in those with stage IVB disease (n=5). Median ΔCt values progressively decreased with increasing clinical stage, indicating a numerical trend toward higher FOXM1 expression in advanced disease. However, the Kruskal–Wallis test showed no statistically significant difference in FOXM1 expression among the three clinical-stage groups (p = 0.140).

DISCUSSION

Demographic and Clinical Characteristics

In the present study, nasopharyngeal carcinoma (NPC) was more frequently observed in men (71.8%), with a mean age of 49.59 ± 10.67 years. The largest proportion of patients was aged 41–60 years (64.1%). This finding is consistent with previous epidemiological studies demonstrating a higher incidence of NPC among men and a predominance among middle-aged adults. Differences in environmental exposures, genetic susceptibility, and other biological factors have been proposed to contribute to the observed sex and age distribution of NPC (Su et al., 2024; Zhang et al., 2024).

Non-keratinizing squamous cell carcinoma was the predominant histopathological type (82.1%), consistent with the established predominance of this subtype in endemic regions of Southeast and East Asia. The high proportion of non-keratinizing NPC in the present study is also comparable with previous findings from Indonesia (Utomo et al., 2023). Clinically, T4 was the most frequent primary tumor category (46.2%), while N1 was the most common regional lymph node category. The predominance of advanced primary tumors is consistent with previous reports showing that NPC is frequently diagnosed at an advanced stage (Alsavaf et al., 2025). The anatomical location of the nasopharynx and nonspecific early symptoms may contribute to delayed diagnosis. This advanced clinical profile provides an important context for evaluating the potential association between FOXM1 expression and disease progression.

FOXM1 Gene Expression in Patients with Nasopharyngeal Carcinoma

In the present study, the mean ΔCt value of FOXM1 was 7.05 ± 3.38, with a median of 6.01 and a range of −1.96 to 13.86. The wide range indicates considerable heterogeneity in FOXM1 expression among patients with NPC. Because lower ΔCt values indicate higher gene expression, the negative ΔCt value observed in one patient suggests relatively high FOXM1 expression in that sample.

Variability in FOXM1 expression may reflect differences in tumor biology, histopathological characteristics, clinical stage, and other molecular factors. These findings are consistent with Pan et al. (2025), who reported higher FOXM1 expression in NPC tissue compared with normal nasal mucosa. (Pan et al., 2025).

The biological role of FOXM1 in NPC progression has been demonstrated in several molecular studies. FOXM1 promotes tumor cell proliferation and may contribute to metabolic reprogramming through the PDK1 pathway, thereby enhancing glycolysis and tumor growth. In addition, FOXM1 has been associated with cellular migration and invasion, supporting its potential role in aggressive tumor behavior (Pan et al., 2025; Zhang et al., 2024). Yang et al. (2022) further demonstrated that USP21 regulates FOXM1 expression and that restoration of FOXM1 can recover several malignant characteristics of NPC cells, suggesting that FOXM1 contributes to the maintenance of an aggressive tumor phenotype (Yang et al., 2022).

Recent evidence has also suggested a potential prognostic role of FOXM1 in NPC. Liang et al. (2026) identified FOXM1 as one of the key genes in the qMIDSKNF biomarker panel and reported its association with tumor progression and more advanced disease (Liang et al., 2026). Similarly, circFOXM1 has been reported to be overexpressed in NPC and associated with advanced clinical stage and poorer prognosis (Pei et al., 2022).

Association Between FOXM1 Gene Expression and Histopathological Type in Patients with Nasopharyngeal Carcinoma

In the present study, patients with non-keratinizing squamous cell carcinoma (SCC) had a lower mean ΔCt value for FOXM1 (6.67 ± 3.24) than those with undifferentiated carcinoma (8.78 ± 3.75), indicating numerically higher FOXM1 expression in non-keratinizing SCC. The difference in ΔCt values was 2.11; however, the difference was not statistically significant ($p = 0.136$). Therefore, no significant association between FOXM1 expression and histopathological type could be established in this study.

Nevertheless, the higher FOXM1 expression observed in non-keratinizing SCC may be biologically relevant. FOXM1 is a transcription factor involved in cell proliferation and cell-cycle regulation and is frequently overexpressed in various malignancies. Its role in regulating genes involved in cell division, invasion, and malignant transformation may contribute to aggressive tumor characteristics (Eide et al., 2022). FOXM1 has also been associated with proliferation, DNA repair, angiogenesis, and inhibition of apoptosis, supporting its role in tumor progression (Schuller et al., 2022). Overall, although FOXM1 expression was numerically higher in non-keratinizing SCC than in undifferentiated carcinoma, the absence of a statistically significant difference indicates that histopathological type was not significantly associated with FOXM1 expression.

Association Between FOXM1 Gene Expression and Primary Tumor Extension in Patients with Nasopharyngeal Carcinoma

In the present study, FOXM1 ΔCt values varied across the T categories without a consistent linear pattern. FOXM1 expression was relatively higher in T1, decreased in T2, and increased again in T3 and T4. However, the Kruskal–Wallis test showed no statistically significant difference among the T categories ($p = 0.255$), indicating that FOXM1 expression was not significantly associated with the extent of primary tumor invasion in this study.

These findings differ from studies in other malignancies that have demonstrated a role for FOXM1 in tumor invasion. In lung adenocarcinoma, high FOXM1 expression has been associated with poorer prognosis and increased tumor cell migration, while FOXM1 knockdown significantly reduced cell migration, suggesting a role in invasive tumor behavior (Li et al., 2023). FOXM1 may promote tumor invasion through epithelial–mesenchymal transition (EMT), characterized by

increased mesenchymal markers such as vimentin and N-cadherin and decreased expression of the epithelial marker E-cadherin. FOXM1 has also been reported to act synergistically with CENPF in promoting tumor proliferation and migration (Dilmac et al., 2024).

Although these molecular findings support a potential role for FOXM1 in tumor invasion and metastasis, the absence of a significant association with T classification in the present study suggests that FOXM1 expression alone may not adequately reflect the extent of primary tumor invasion in this NPC cohort. Other molecular and clinical factors may contribute to local tumor progression (Liu et al., 2024).

Association Between FOXM1 Gene Expression and Regional Lymph Node Involvement in Nasopharyngeal Carcinoma

In the present study, FOXM1 ΔCt values varied across the N categories without a clear linear trend. N0 showed the lowest ΔCt value (1.67), indicating relatively higher FOXM1 expression, whereas N2 showed a median ΔCt of 6.16 with a wide range, indicating substantial variability. The Kruskal–Wallis test demonstrated a statistically significant difference among the N categories ($p = 0.022$), indicating that FOXM1 expression was significantly associated with regional lymph node involvement in this cohort.

The association between FOXM1 expression and regional lymph node involvement observed in the present study may reflect the role of FOXM1 in promoting an aggressive tumor phenotype. FOXM1 is a transcription factor involved in several processes underlying tumor progression and metastasis, including cell proliferation, epithelial–mesenchymal transition, migration, and invasion. In particular, FOXM1 has been reported to regulate matrix metalloproteinases, including MMP-2 and MMP-9, which contribute to extracellular matrix degradation and facilitate tumor cell invasion. Experimental evidence has further demonstrated that FOXM1 can directly promote MMP-2 transcription and enhance the migratory and invasive capacity of tumor cells (Zhang et al., 2021; Khan et al., 2023). However, the absence of a clear linear trend across the N categories in the present study suggests that FOXM1 expression alone may not determine the extent of lymph node involvement. Lymph node metastasis is a complex multistep process influenced by interactions between tumor cells, the lymphatic system, immune factors, and the tumor microenvironment. Therefore, FOXM1 may contribute to the biological processes associated with lymphatic dissemination, but should not be considered the sole determinant of regional lymph node metastasis.

Previous studies have reported inconsistent associations between FOXM1 expression and lymph node metastasis. Cheng et al. (2020) suggested that FOXM1 acts primarily as an upstream molecular regulator of tumor aggressiveness, whereas lymph node metastasis is influenced by multiple biological factors. More recent evidence has demonstrated that FOXM1 promotes tumor progression through mechanisms involving cell proliferation, migration, invasion, and epithelial–mesenchymal transition, which may contribute to metastatic spread (Khan et al., 2023). Conversely, the relationship between FOXM1 expression and lymph node involvement may not be proportional to the extent of nodal disease, as lymph node metastasis is a complex multistep process involving tumor cells, lymphatic vessels, immune responses, and the tumor microenvironment. Therefore, the significant association observed in the present study supports a potential role of FOXM1 in the biological processes underlying lymphatic dissemination, while the absence of a clear linear pattern across the N categories suggests that lymph node involvement is likely influenced by additional clinical and molecular factors.

Association Between FOXM1 Gene Expression and Regional Lymph Node Involvement in Nasopharyngeal Carcinoma

In the present study, FOXM1 ΔCt values varied across the N categories without a clear linear trend. N0 had the lowest ΔCt value (1.67), indicating high FOXM1 expression, while N1 and N3 showed

similar mean values. N2 had a median ΔCt value of 6.16 with a wide variation, indicating substantial heterogeneity. The Kruskal–Wallis test showed a statistically significant difference among the groups (p = 0.022), indicating a significant association between FOXM1 expression and the degree of lymph node metastasis.

In a multivariate analysis, factors such as *vasculogenic mimicry*, β-catenin, Tcf4, and tumor stage (pTNM) were identified as independent prognostic factors, together with lymph node metastasis. In this context, FOXM1 acts more as an upstream molecular regulator influencing signaling pathways and tumor aggressiveness rather than as a direct clinical indicator of lymph node involvement. Although FOXM1 is closely associated with tumor biological mechanisms, its relationship with clinical parameters such as lymph node enlargement may be indirect. Lymph node metastasis is a complex process involving interactions between tumor cells, the lymphatic system, immune factors, and the tumor microenvironment (Cheng et al., 2020).

Furthermore, a study in patients with early-stage esophageal cancer showed that FOXM1 expression was not always directly associated with lymph node involvement but was more closely related to tumor size (p = 0.024), depth of invasion (p = 0.048), and degree of differentiation (p = 0.043). In that study, all patients were N0, without lymph node metastasis, but significant variation in FOXM1 expression was still observed among patients. Recent evidence suggests that FOXM1 contributes to tumor aggressiveness through multiple biological processes, including cell proliferation, epithelial–mesenchymal transition, migration, and invasion, which may facilitate metastatic dissemination. However, the extent of lymph node metastasis is influenced by multiple interacting molecular and microenvironmental factors and therefore may not demonstrate a consistent linear relationship with FOXM1 expression. Thus, the significant association observed in the present study supports the potential involvement of FOXM1 in lymphatic dissemination, while the absence of a clear linear trend across the N categories suggests that FOXM1 expression alone is unlikely to determine the extent of regional lymph node metastasis (Khan et al., 2023).

Association Between FOXM1 Gene Expression and Tumor Metastasis in Patients with Nasopharyngeal Carcinoma

In the present study, the median ΔCt value of FOXM1 was lower in patients with distant metastasis (M1) than in those without distant metastasis (M0). However, no statistically significant association was found. This may be related to the relatively small number of patients in the M1 group (n = 5) compared with the M0 group (n = 34), which may reduce statistical power. The wide variation in the M0 group (range −1.96 to 13.86) also indicates heterogeneity in FOXM1 expression among patients. FOXM1 is a member of the Forkhead Box family that regulates genes involved in the G2/M cell-cycle phase. FOXM1 activation can increase the expression of cyclin B1, PLK1, and Aurora kinase, which support tumor cell proliferation. FOXM1 also interacts with the PI3K/AKT, Wnt/β-catenin, and TGF-β signaling pathways involved in invasion and metastasis. In NPC, FOXM1 expression has been reported to be increased in tumor tissue compared with normal nasopharyngeal tissue and associated with advanced disease and tumor aggressiveness (Liu et al., 2024).

FOXM1 may promote tumor cell migration and invasion through the regulation of matrix metalloproteinases and other molecular pathways involved in extracellular matrix remodeling (Zhang et al., 2021; Khan et al., 2023). Distant metastasis in NPC is multifactorial and is influenced not only by FOXM1 but also by Epstein–Barr virus infection, immune status, tumor hypoxia, the tumor microenvironment, genetic alterations, and other molecular pathways (Liu et al., 2024). Therefore, although the lower ΔCt values observed in the M1 group suggest relatively higher FOXM1 expression, the absence of a statistically significant association indicates that FOXM1 alone may have limited value as a biomarker for predicting distant metastasis.

Association Between FOXM1 Gene Expression and Clinical Stage of Nasopharyngeal Carcinoma

In the present study, FOXM1 ΔCt values varied across clinical stages without a clear linear pattern. The median ΔCt value was 8.78 (range 4.98–12.52) in stages II and III (n = 10), decreased to 6.28 (range −1.96–13.86) in stage IVA (n = 23), and reached 5.39 (range 4.92–12.20) in stage IVB (n = 5). However, the Kruskal–Wallis test showed no statistically significant difference among clinical stages (p = 0.140), indicating that FOXM1 expression was not significantly associated with clinical stage in this study.

Bioinformatic studies have shown that although FOXM1 is frequently increased in various cancers, its clinical significance for patient outcomes may vary among cancer types (Rida et al., 2024). Yang et al. (2022) reported that the role of FOXM1 in NPC was more prominent in tumor metabolism and cell proliferation than as a direct indicator of clinical stage. FOXM1 regulates glycolysis through PDK1 activation, increases energy production in tumor cells, and promotes cell proliferation and progression. Although FOXM1 expression was associated with poorer prognosis, a direct linear relationship with clinical stage was not consistently demonstrated (Yang et al., 2022).

FOXM1 expression may also be influenced by isoform variation resulting from alternative splicing. The main FOXM1 isoforms, FOXM1a, FOXM1b, and FOXM1c, have different biological functions. FOXM1b and FOXM1c are transcriptionally active and regulate cell-cycle genes, whereas FOXM1a does not exhibit the same transcriptional activity toward most FOXM1 target genes (Jia et al., 2023).

In contrast, several clinical studies have demonstrated a significant association between FOXM1 expression and NPC stage. FOXM1 expression was also increased in NPC tissue compared with normal tissue and was associated with invasive characteristics, including stromal and vascular infiltration, particularly in T4 disease (Yu et al., 2021). Experimental findings by Yu et al. (2021) further showed that FOXM1 contributes to tumorigenesis through activation of the Wnt/β-catenin pathway, while FOXM1 inhibition reduced tumor cell viability, increased apoptosis, and inhibited tumor growth (Yu et al., 2021).

Based on these findings, although several studies have demonstrated an association between FOXM1 expression and NPC stage, this relationship is not consistently significant across all parameters. FOXM1 appears to have a stronger role in biological processes such as proliferation, metabolism, invasion, and metastasis than as a direct indicator of clinical stage. Therefore, FOXM1 expression as a biomarker of disease stage should be interpreted cautiously and combined with other clinical factors to provide a more comprehensive assessment of disease progression (Yang et al., 2022).

CONCLUSION

FOXM1 mRNA expression was not significantly associated with the clinical stage of nasopharyngeal carcinoma. However, FOXM1 expression demonstrated a significant association with regional lymph node involvement, although no significant associations were observed with histopathological type, primary tumor extension, or distant metastasis. The progressive decrease in median ΔCt values from earlier to more advanced clinical stages indicates a numerical trend toward higher FOXM1 expression in advanced disease. These findings suggest that FOXM1 may be involved in the biological processes underlying tumor progression, particularly regional lymphatic dissemination, but its expression alone may not be sufficient as a biomarker for clinical staging in nasopharyngeal carcinoma.

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