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PROGNOSTIC SIGNIFICANCE OF HYPOXIA-INDUCIBLE FACTOR-1 α EXPRESSION IN UROTHELIAL CARCINOMA OF THE URINARY BLADDER: A PROSPECTIVE FOLLOW-UP STUDY

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ABSTRACT

Background: Urothelial carcinoma of the urinary bladder is a common malignancy with heterogeneous clinical behavior, ranging from superficial disease to aggressive invasive cancer. Tumor hypoxia is an important microenvironmental factor influencing progression and therapeutic resistance. Hypoxia-inducible factor-1α (HIF-1α) is a key regulator of cellular adaptation to hypoxia and has been implicated in tumor aggressiveness and prognosis across several solid malignancies. The study aimed to determine the prognostic significance of HIF-1α immunohistochemical expression in urothelial carcinoma of the urinary bladder. Objectives were to evaluate its association with recurrence, metastasis, and patient survival during follow-up. **Materials and Methods:** This prospective follow-up study included 46 histologically confirmed cases of urothelial carcinoma with available one-year follow-up data. HIF-1α expression was assessed by immunohistochemistry on tumor specimens and categorized by intensity. Patients were followed through outpatient visits and telephonic records to document recurrence, metastasis, and survival. Associations between HIF-1α expression and outcomes were analyzed using appropriate statistical tests. **Result:** The cohort showed male predominance and a higher frequency of high-grade and invasive tumors. At one-year follow-up, recurrence occurred in 32.61% of cases, metastasis in 17.39%, and mortality in 32.61%. Higher HIF-1α expression showed a trend toward increased recurrence, metastasis, and mortality; however, no statistically significant association was observed between HIF-1α expression and these outcomes ($p > 0.05$). **Conclusion:** Although increased HIF-1α expression demonstrated a trend toward adverse clinical outcomes, it did not show a statistically significant prognostic association in this short-term follow-up study. Larger studies with longer follow-up are required to clarify its prognostic value.

INTRODUCTION

Urothelial carcinoma of the urinary bladder represents one of the most common malignancies of the urinary tract, characterized by variable clinical outcomes that range from indolent superficial disease to rapidly progressing invasive cancer.[1] Tumor behaviour in bladder cancer is influenced not only by traditional clinicopathological features such as stage and grade but also by underlying molecular and micro-environmental factors. Among these, the presence of hypoxia—a state of reduced oxygen availability within the tumour microenvironment—is recognized as a fundamental driver of aggressive tumour biology.[2]

Hypoxia arises as tumour growth outpaces the development of an effective vascular supply, creating regions where oxygen supply is insufficient relative to demand. Cellular adaptation to this hypoxic stress is mediated by complex regulatory mechanisms that reprogram tumour metabolism, promote angiogenesis, and enable survival under adverse conditions.[3] Central to these adaptive responses is hypoxia-inducible factor-1 (HIF-1), a heterodimeric transcription factor that regulates the expression of numerous genes responsible for

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metabolic adaptation, neovascularization, and cell survival.[4] The alpha subunit of this complex, hypoxia-inducible factor-1α (HIF-1α), is rapidly degraded under normal oxygen conditions but becomes stabilized and transcriptionally active in hypoxia, allowing it to bind hypoxia-responsive elements in target gene promoters and drive expression of factors such as vascular endothelial growth factor (VEGF) and glycolytic enzymes that facilitate tumour progression.[5]

Elevated expression of HIF-1α has been documented across a spectrum of solid tumours and is closely associated with adverse biological behaviour. In bladder cancer specifically, immunohistochemical studies have demonstrated a positive relationship between HIF-1α expression and aggressive tumour characteristics, including higher histological grade and advanced clinical stage.[6] Overexpression of HIF-1α correlates with increased angiogenesis and enhanced microvessel density, reflecting its role in orchestrating vascular responses that support tumour growth.[7] Moreover, several investigations have reported that patients with higher levels of HIF-1α expression in tumour tissues exhibit poorer overall survival and disease-free survival compared with those with lower expression, suggesting that HIF-1α may serve as a marker of unfavourable prognosis.[8]

The biological relevance of HIF-1α in bladder cancer extends beyond its association with histopathological features; it also intersects with critical mechanisms of therapeutic resistance.[9] Hypoxia and HIF-1α activation have been implicated in reduced sensitivity to radiotherapy and certain chemotherapeutic agents, partly through the up-regulation of survival pathways and adaptive metabolic changes that diminish the effectiveness of cytotoxic stress. Studies in other tumour types indicate that high HIF-1α levels can modify responses to treatment, an effect that may have implications for therapy selection and outcome prediction in bladder cancer.[7] While some research in non-bladder cancers has shown improved locoregional control with hypoxia modification in patients exhibiting high HIF-1α expression, the translation of these findings into routine clinical practice for bladder cancer remains an ongoing area of investigation.[10]

Despite the growing body of evidence linking HIF-1α to tumour aggression and survival outcomes, its precise prognostic value in urothelial carcinoma has not been conclusively determined in prospectively followed patient cohorts.[11] Retrospective analyses and smaller observational studies have provided important insights, but they are limited by heterogeneity in study design, patient populations, and endpoints.[12] Furthermore, the interplay between HIF-1α expression and other molecular and environmental determinants of tumour behaviour—such as angiogenic factors, metabolic regulators, and immune infiltration—is complex, underscoring the need for structured prospective evaluation to clarify the independent prognostic significance of HIF-1α in this disease.[13]

There is a clear imperative to investigate HIF-1α expression in urothelial carcinoma within the context of a carefully designed prospective study with longitudinal follow-up. Evaluating HIF-1α both as a biomarker of tumour biology and as a potential predictor of clinical outcomes may enhance existing prognostic frameworks, refine risk stratification, and ultimately support more individualized therapeutic decision-making.[14] By systematically correlating HIF-1α expression with patient outcomes over time, this study aims to elucidate whether HIF-1α can reliably supplement standard histopathological parameters for prognostication and serve as a foundation for future biomarker-driven strategies in the management of bladder cancer patients.[9]

The study aimed to determine the prognostic significance of hypoxia-inducible factor-1α immunohistochemical expression in urothelial carcinoma of the urinary bladder during follow-up, with objectives to evaluate its association with clinical outcomes such as recurrence and metastasis, and to assess the relationship between HIF-1α expression levels and patient survival over the follow-up period.

MATERIALS AND METHODS

This prospective follow-up study included 46 patients with urothelial carcinoma of the urinary bladder who were available for clinical follow-up for one year. Baseline clinicopathological data and HIF-1α immunohistochemical expression scores were obtained from initial histopathological evaluation. Patients were followed through outpatient visits and telephonic communication to assess recurrence, metastasis, and survival status. Associations between HIF-1α expression and clinical outcomes were analyzed. Statistical analysis was carried out using SPSS software, and categorical variables were compared using the chi-square test, with a p-value less than 0.05 considered statistically significant.

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RESULTS

Table 1: Baseline Clinicopathological Characteristics of Follow-up Cohort (n = 46)

Variable	Category	Number (n)	Percentage (%)
Age group (years)	≤ 40	4	8.7
	41–50	10	21.7
	51–60	15	32.6
	61–70	14	30.4
	> 70	3	6.6
Gender	Male	40	87.0
	Female	6	13.0
Tumor grade	Low grade	14	30.4
	High grade	32	69.6
Depth of invasion	Superficial	9	19.6
	Lamina propria invasion	25	54.3
	Muscle invasion	12	26.1

The follow-up cohort mainly included patients aged 51–70 years, with a clear male predominance (87%). High-grade tumors were common, comprising nearly two-thirds of cases, indicating aggressive disease biology. Most patients showed invasive disease, particularly lamina propria and muscle invasion, highlighting advanced tumor behavior in the follow-up population. Overall, the cohort reflects a predominantly male, older population with high-grade and deeply invasive bladder tumors.

Follow-up was available for 46 cases up to one year through telephonic contact and OPD records, while the remaining cases were lost to follow-up. Metastasis was observed in 8 cases (17.39%) and recurrence in 15 cases (32.61%). Overall, 31 patients (67.39%) survived, whereas 15 (32.61%) died during the study period.

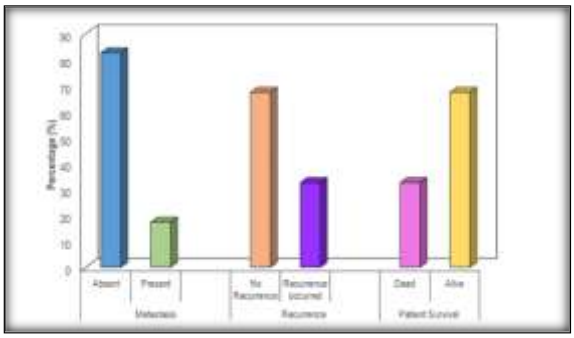

Figure 1: Distribution of study population according to bladder cancer follow up.

Table 2: Association of HIF-1α Immunohistochemical Expression with Tumor Recurrence at 1-Year Follow-up (n = 46)

HIF-1α Expression Category	Recurrence Present n (%)	No Recurrence n (%)	Total (n)	p-value
Negative	5 (19.2)	16 (61.5)	21	
Weak	2 (7.7)	4 (15.4)	6	
Moderate	4 (15.4)	9 (34.6)	13	
Strong	4 (15.4)	2 (7.7)	6	
Total	15 (32.6)	31 (67.4)	46	>0.05

At 1-year follow-up, tumor recurrence was observed in approximately one-third of patients, while the majority remained recurrence-free. Recurrence occurred across all HIF-1α expression categories, with no consistent trend toward increasing recurrence with higher expression levels. Although strong expression showed proportionally fewer non-recurrence cases, the overall association between HIF-1α immunohistochemical expression and tumor recurrence was not statistically significant ($p > 0.05$). These findings suggest that HIF-1α expression alone was not a reliable predictor of short-term recurrence in this cohort.

Table 4: Association of HIF-1α Immunohistochemical Expression with Metastasis at 1-Year Follow-up (n = 46)

HIF-1α Expression Category	Metastasis Present n (%)	Metastasis Absent n (%)	Total (n)	p-value
Negative	2 (7.7)	19 (73.1)	21	
Weak	1 (3.8)	5 (19.2)	6	
Moderate	2 (7.7)	11 (42.3)	13	
Strong	3 (11.5)	3 (11.5)	6	
Total	8 (17.4)	38 (82.6)	46	>0.05

At 1-year follow-up, metastasis was documented in a minority of patients, while the majority remained metastasis-free. Metastatic events were observed across all HIF-1α expression categories, with slightly higher proportions in cases showing strong expression. However, statistical analysis demonstrated no significant association between HIF-1α immunohistochemical expression and the occurrence of metastasis ($p > 0.05$). These results indicate that HIF-1α expression did not independently predict metastatic risk within the follow-up period.

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Table 5: Association of HIF-1α Immunohistochemical Expression with Patient Survival at 1-Year Follow-up (n = 46)

HIF-1α Expression Category	Alive n (%)	Dead n (%)	Total (n)	p-value
Negative	16 (34.8)	5 (10.9)	21	
Weak	4 (8.7)	2 (4.3)	6	
Moderate	8 (17.4)	5 (10.9)	13	
Strong	3 (6.5)	3 (6.5)	6	
Total	31 (67.4)	15 (32.6)	46	>0.05

At 1-year follow-up, approximately two-thirds of patients were alive, while one-third had died, reflecting substantial short-term mortality. Survival was observed across all HIF-1α expression categories, with no clear gradient between negative, weak, moderate, or strong expression groups. Although proportionally higher deaths were noted in moderate and strong expression categories, this trend did not reach statistical significance. Overall, HIF-1α immunohistochemical expression showed no significant association with patient survival ($p > 0.05$).

DISCUSSION

Despite advances in diagnosis and management, urothelial carcinoma of the urinary bladder continues to exhibit high rates of recurrence, progression, and disease-related mortality. Identification of reliable prognostic biomarkers capable of predicting adverse outcomes remains a clinical priority.[15] HIF-1α has emerged as a potential prognostic indicator due to its central role in hypoxia-induced angiogenesis, tumor survival, and metastatic potential.[16]

In the present follow-up study, higher HIF-1α expression was associated with increased rates of tumor recurrence, metastasis, and mortality, although these associations did not reach statistical significance. These findings are comparable to those of Theodoropoulos VE et al. (2005), who demonstrated that overexpression of HIF-1α in superficial urothelial carcinoma predicted higher recurrence rates and progression to high-grade disease. Similarly, Palit V et al. (2005) reported a significant association between HIF-1α expression and recurrence as well as reduced survival in superficial bladder cancer.[17,18]

The trend toward higher metastatic rates among patients with strong HIF-1α expression observed in this study is supported by experimental evidence from Kondo Y et al. (2005), who demonstrated that overexpression of HIF-1α enhanced tumor growth, angiogenesis, and resistance to hypoxic stress in bladder cancer cell lines. Furthermore, Ke HL et al. (2008) reported that high HIF-1α expression was a significant predictor of cancer-specific survival and tumor recurrence in urothelial carcinoma of the upper urinary tract.[19,20]

The association between HIF-1α expression and poorer survival outcomes observed in the present study aligns with findings by Chai CY et al. (2008) and Hunter BA et al. (2014), who identified HIF-1α as an independent prognostic factor and demonstrated improved treatment response in patients with high HIF-1α expression receiving hypoxia-modifying therapy. These studies collectively suggest that HIF-1α not only reflects tumor hypoxia but may also influence therapeutic response and long-term outcomes. Although statistical significance was not achieved in the present study, this may be attributed to the limited follow-up duration and relatively small sample size. Nevertheless, the consistent trend toward adverse outcomes in patients with higher HIF-1α expression underscores its potential prognostic relevance. Larger prospective studies with longer follow-up are warranted to further validate HIF-1α as a prognostic biomarker and to explore its role as a potential therapeutic target in urothelial carcinoma.[7,21]

CONCLUSION

In conclusion, this prospective follow-up study evaluated the prognostic significance of HIF-1α immunohistochemical expression in urothelial carcinoma of the urinary bladder. Although higher HIF-1α expression showed a consistent trend toward increased recurrence, metastasis, and mortality, these associations did not achieve statistical significance during the one-year follow-up period. The findings suggest that HIF-1α alone may not serve as a reliable short-term prognostic marker. However, its observed association with adverse outcomes indicates potential biological relevance. Larger studies with extended follow-up and integrated molecular profiling are required to clarify its independent prognostic value and clinical utility.

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