International Medicine
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Research Article

Section: Pathology

Role of Immunohistochemical Expression of P-53 and HER-2-NEU in Understanding the Pathogenesis and Prognosis of Gall Bladder Carcinoma

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ARTICLE INFO

Article History:
Received: 08-09-2024
Accepted: 11-10-2024

Keywords:
Gallbladder carcinoma
p53
HER2/neu
Histopathology
Immunohistochemistry
Tumor progression
Targeted therapy

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ABSTRACT

Introduction: Gallbladder carcinoma (GBC) is a highly lethal malignancy, often diagnosed at advanced stages due to its asymptomatic nature in the early phases. Histopathological evaluation and the expression of molecular markers, such as p53 and HER2/neu, play critical roles in understanding GBC's pathogenesis, guiding treatment, and evaluating prognosis. **Objective:** The study aimed to evaluate the role of immunohistochemical expression of p53 and HER2/neu in gallbladder carcinoma **Methods:** A two-year prospective cross-sectional study was conducted at GSVM Medical College and LLR Hospitals, Kanpur. Histopathological examination and immunohistochemical analysis of p53 and HER2/neu were performed on gallbladder carcinoma and precursor lesions. Statistical associations were assessed using the Chi-squared test. **Results:** The study included 50 patients, with 42 HER2/neu positive and 8 HER2/neu negative cases. Tumor size showed a significant association with HER2/neu expression (p-value = 0.0151), while no significant association was found for tumor site (p-value = 1.0) or regional lymph node involvement (p-value = 0.3488). For p53, 44 cases were positive, and 6 were negative, with significant associations found with histological grade (p-value = 0.04). No significant association was observed with tumor size or site distribution by p53 status. **Conclusion:** The study highlights the importance of p53 and HER2/neu in GBC's pathogenesis. While HER2/neu expression was significantly associated with tumor size, p53 was associated with histological grade. These findings suggest the potential for these markers to inform treatment strategies and prognostic assessments in GBC.

INTRODUCTION

Gallbladder carcinoma (GBC) is a highly lethal malignancy often diagnosed in its later stages due to its undetectable nature in the early stages. This delayed diagnosis contributes to its poor prognosis. Histopathological evaluation is essential for diagnosing GBC, determining its stage, and guiding treatment strategies [1]. Typically, this involves examining tissue samples obtained through biopsy or surgical resection under a microscope. This evaluation identifies the specific type of carcinoma, such as adenocarcinoma, squamous cell carcinoma, or Aden squamous carcinoma, based on cellular morphology. It also assesses the degree of differentiation of tumor cells, the extent of tumor invasion into the gallbladder wall, involvement of the lymph nodes, and distant metastasis. Additionally, precursor lesions like dysplasia and carcinoma in situ are identified and evaluated, offering insights into the carcino genesis process [2].

The p53 gene, a crucial tumor suppressor, plays a vital role in regulating the cell cycle and preventing genomic mutations. Mutations in p53 are among the most common genetic changes observed in various carcinomas, including GBC. These mutations can cause a loss of p53's tumor-suppressive functions, leading to uncontrolled cell proliferation and the survival of cells with damaged DNA. Immunohistochemical studies often reveal overexpression of mutant p53 protein in GBC, serving as a marker for diagnosis and prognosis. These mutations are frequently associated with higher tumor grades, advanced stages, and poor outcomes in GBC patients [3].

HER-2-neu (human epidermal growth factor receptor 2) is another important protooncogene that encodes a transmembrane tyrosinekinase receptor involved in cell growth and differentiation.

Overexpression or amplification of HER-2-neu is widely implicated in the pathogenesis of several cancers, including GBC. This overexpression or gene amplification can result in increased signaling for cell proliferation and survival contributing to tumor development [4]. Techniques like immunohistochemistry and fluorescence in situ hybridization (FISH) are commonly used to detect HER-2-neu status in GBC, aiding in diagnosis and potentially guiding targeted therapy. HER-2-neu overexpression in GBC is often linked with aggressive tumor behavior advanced stage, and poor clinical outcomes. Targeted therapies such as trastuzumab, which have shown promise in other cancers are also being explored in clinical trials for GBC [5].

Precursor lesions, which are abnormal tissue changes that precede invasive carcinoma, are significant in GBC. These include dysplasia, gallbladder adenomas, and carcinoma in situ. Dysplastic changes in gallbladder epithelia are characterized by cellular atypia and architectural disorg-anization, with high grade dysplasia having a higher risk of progression to carcinoma [6]. Gallbladder adenomas which are benign epithelial tumors, can undergo malignant transformation particularly those with a higher grade of dysplasia. Carcinoma in situ represents a localized non invasive stage of carcinoma confined to the epithelium, with the potential to progress to invasive GBC [7].

The expression of p53 and HER-2-neu in GBC and its precursor lesions provides valuable insights into the molecular mechanisms driving this malignancy and offers potential targets for therapeutic intervention. Understanding these factors can enhance prognostic assessments and guide personalized treatment approaches for GBC patients [8].

GBC is a deadly malignancy with a generally poor prognosis, often detected only in later stages due to its typically undetectable nature in the early stages. This type of cancer is more prevalent in specific geographic regions and populations, with risk factors including chronic gallbladder inflammation, gallstones, and certain genetic mutations. The clinical presentation of GBC varies widely, ranging from vague symptoms such as abdominal pain and nausea to more severe signs like jaundice and weight loss, which often appear only when the disease is advanced [9].

Histopathological evaluation is crucial for diagnosing GBC. This process involves the microscopic examination of tissue samples obtained through biopsy or surgical resection. Histopathology not only verifies the presence of cancer cells but also provides detailed information about the histological type and grade of carcinoma, which is essential for determining the most effective treatment strategy. Adenocarcinoma is the most common histological type of GBC, but other types, such as squamous cell carcinoma and adenosquamous carcinoma, can also occur. Each type can behave differently and may require different treatment approaches [10]. Additionally, histopathological evaluation helps stage the disease by assessing the extent of tumor invasion into the gallbladder wall, lymph node involvement, and the presence of distant metastasis. This staging is critical for predicting prognosis and planning treatment, which may include surgery, chemotherapy, and radiation therapy [11].

Histopathological evaluation of gallbladder carcinoma (GBC) is crucial for diagnosing and staging the disease, identifying precursor lesions like dysplasia and carcinoma in situ, and guiding treatment strategies. Recent research focuses on the molecular markers p53 and HER-2-neu which play significant roles in GBC's pathogenesis and may serve as biomarkers and therapeutic targets [12]. Advances in genomic and proteomic technologies are refining the understanding of these markers, leading to more precise characterizations and the development of targeted therapies. Ongoing studies, including those exploring the combination of HER-2-neu inhibitors with other treatments, aim to overcome resistance and improve treatment efficacy. The growing body of evidence highlights the potential for personalized therapeutic approaches, enhancing prognosis and treatment outcomes for GBC patients [13].

The study aims to examine the expression of p53 and Her2neu in gallbladder carcinoma and its precursor lesions. The primary objective is to evaluate the histopathological features of gallbladder carcinoma, while the secondary objective focuses on analyzing the immunohistochemical expression of p53 and Her2neu in both gallbladder carcinoma and its precursor lesions.

MATERIAL & METHODS

This two-year prospective cross sectional study was conducted in the Department of Pathology, in collaboration with the Postgraduate Department of Surgery at GSVM Medical College and LLR & Associated Hospitals, Kanpur. The study focused on the histopathological evaluation of gallbladder carcinoma and the role of p53 and HER2NEU in gallbladder carcinoma and its precursor lesions. Ethical approval was obtained from GSVM Medical College, and all participants provided written informed consent. Inclusion criteria included cases of gallbladder carcinoma while exclusion criteria were secondary carcinoma of the gallbladder and patients who had received chemotherapy or radiotherapy.

RESULTS

In the distribution of tumor sites between the Body and Fundus among patients, there were 2 males and 6 females with tumors in the Body, and 9 males and 33 females with tumors in the Fundus, totaling 8 and 39 patients, respectively. The Chi-squared test showed no significant association between tumor site and sex (p-value = 1.0). The mean age was 60.09 years for males and 54.87 years for females, with an overall mean of 56.02 years across 50 patients. Regarding P53 IHC status, 44 patients were P53 positive and 6 were P53 negative, with no significant association between age group or sex and P53 status (both p-values = 1.0).

Table 1: pTNM Staging Distribution by HER2NEU IHC Status

pTNM STAGING	HER2NEU IHC			Test Name	P value
	Positive N	Negative N	Total N		
pT1NxMx	6	1	7	Chi-squared	0.1742
pT1bNxMx	33	5	38		
pT2N0Mx	0	1	1		
pT2NxMx	2	1	3		
pT2aNxMx	1	0	1		
Total	42	8	50		

In the distribution of pTNM staging by HER2NEU IHC status, 6 patients with pT1NxMx were HER2NEU positive and 1 was negative; 33 with pT1bNxMx were positive and 5 were negative; 0 with pT2N0Mx were positive and 1 was negative; 2 with pT2NxMx were positive and 1 was negative; and 1 with pT2aNxMx was positive with no negative cases. Overall, 42 cases were HER2NEU positive and 8 were negative. The Chi-squared test yielded a p-value of 0.1742, indicating no statistically significant association between pTNM staging and HER2NEU IHC status.

Table 2 : Regional Lymph Nodes Distribution by HER2NEU IHC Status

Regional lymph nodes	HER2NEU IHC			Test Name	P value
	Positive N	Negative N	Total N		
cannot be assessed	42	7	49	Chi-squared	0.3488
free from tumor	0	1	1		
Total	42	8	50		

In the distribution of regional lymph nodes by HER2NEU IHC status, 42 patients who could not be assessed were HER2NEU positive, while 7 were negative. No patients free from tumor were HER2NEU positive, and 1 was negative, resulting in a total of 42 positive and 8 negative cases. The Chi squared test yielded a p value of 0.3488, indicating no statistically significant association between regional lymph nodes and HER2NEU IHC status.

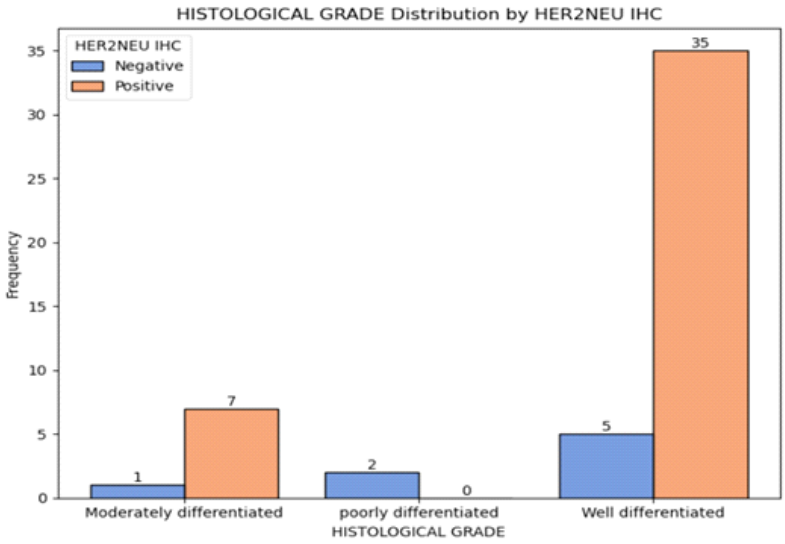

Figure 1: Histological Grade Distribution by HER2NEU IHC Status

In the distribution of histological grades by HER2NEU IHC status, 35 well differentiated cases were HER2NEU positive and 5 were negative. Among moderately differentiated cases, 7 were HER2NEU positive and 1 was negative, while all poorly differentiated cases were HER2NEU negative, with 2cases observed. This resulted in a total of 42 HER2NEU positive and 8 negative cases. The Chi squared test yielded a p value of 0.0042, indicating a statistically significant association between histological grade and HER2NEU IHC status.

Table 3: Histological Type Distribution by HER2NEU IHC Status

Histological Type	HER2NEU IHC			Test Name	P value
	POSITIVE N	Negative N	Total N		
Adenocarclnoma	41	8	49	Chi-squared	1.0
Mucinous Adenocarclnoma	1	0	1		
Total	42	8	50		

In the distribution of histological types by HER2NEU IHC status 41 patients with adenocarcinoma were HER2NEU positive and 8 were negative. Additionally 1 patient with mucinous adenocarcinoma was HER2NEU positive bringing the total to 42 HER2NEU positive and 8 negative cases. The Chi-squared test yielded a p-value of 1.0, indicating no statistically significant association between histological type and HER2NEU IHC status.

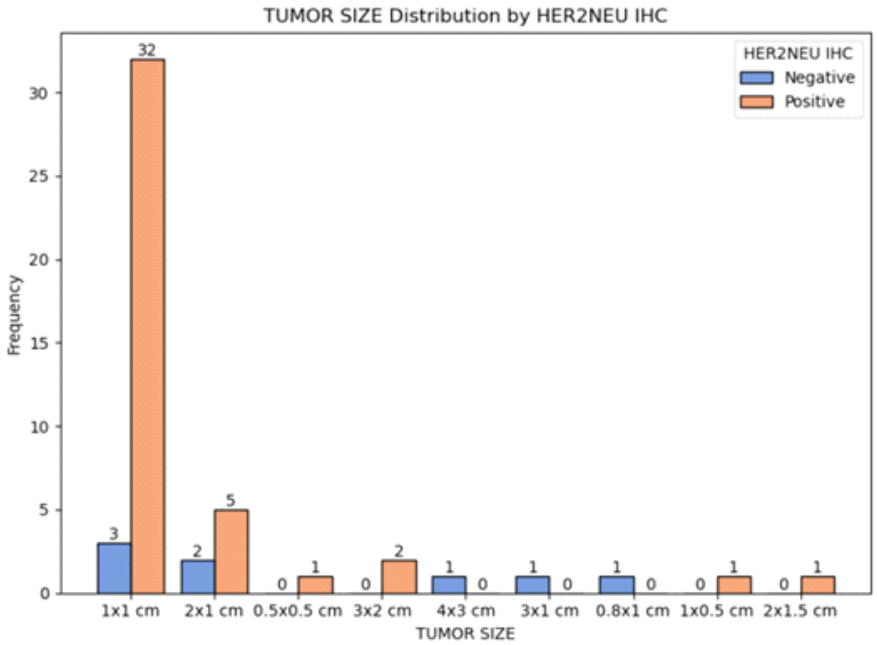

Figure 2: Tumor Size Distribution by HER2NEU IHC Status

In the distribution of tumor size by HER2NEU IHC status 1 patient with a 0.5x0.5 cm tumor was HER2NEU positive, none were negative; for 0.8x1 cm, none were positive and 1 was negative; for 1x0.5 cm, 1 was positive and none were negative; for 1x1 cm, 32 were positive and 3 were negative; for 2x1 cm, 5 were positive and 2 were negative; for 2x1.5 cm, 1 was positive and none were negative; for 3x1 cm, none . were positive and 1 was negative; for 3x2 cm, 2 were positive and none were negative; for 4x3 cm, none were positive and 1 was negative, totaling 42 positive and 8 negative cases. The Chi-squared test yielded a p-value of 0.0151, indicating a statistically significant association between tumor size and HER2NEU IHC status

Table 4 :Tumor Site Distribution by HER2NEU IHC Status

TUMOR SITE	HER2NEU IHC			Test Name	P value
	Positive N	Negative N	Total N		
Body	7	1	8	Chi-squared	1.0
Fundus	35	7	42		
Total	42	8	50		

In the distribution of tumor site by HER2NE IHC status 7 patients with tumors in the body were HER2NEU positive, and 1 was negative. For tumors in the fundus, 35 patients were HER2NEU positive, and 7 were negative, totaling 42 positive and 8 negative cases. The Chi squared test resulted in a p-value of 1.0, indicating no statistically significant association between tumor site and HER2NEU IHC status.

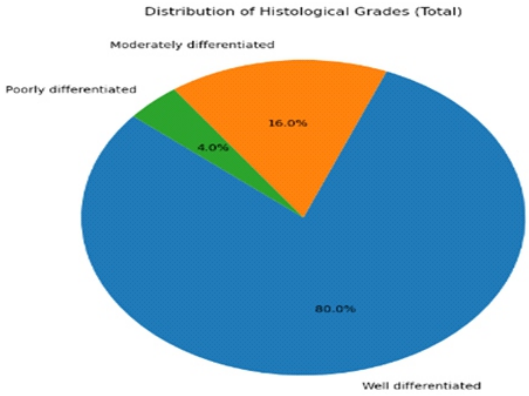

Figure 3: Histological Grade Distribution by P53 IHC Status

In the distribution of histological grades by P53 IHC status, 34 well-differentiated cases were P53 positive, and 6 were P53 negative. Among moderately differentiated cases, 8 were P53 positive, and all poorly differentiated cases (2 in total) were P53 positive. This resulted in a total of 44 P53 positive and 6 P53 negative cases. The Chi-squared test yielded a p value of 0.04, indicating a significant association between histological grade and P53 IHC status.

Table 5:Tumor Size Distribution by P53 IHC Status

Tumor size	P53 IHC			Test Name	P value
	Positive N	Negative N	Total N		
0.5 x 0.5 cm	1	0	1	Chi-squared	0.4016
0.8x1 cm	1	0	1		
1x0.5 cm	1	0	1		
1x1 cm	31	4	35		
2x1 cm	6	1	7		
2x1.5 cm	1	0	1		
3x1 cm	1	0	1		
3x2 cm	2	0	2		
4x3 cm	0	1	1		
Total	44	6	50		

In the distribution of tumor size by P53 IHC status, 1 patient with a 0.5x0.5 cm tumor was P53 positive as were patients with 0.8x1 cm, 1x0.5 cm, 2x1 cm, 2x1.5 cm, and 3x1 cm tumors. For 1x1 cm tumors, 31 were P53 positive and 4 were negative. For 2x1 cm tumors 6 were positive, and 1 was negative. For 3x2 cm tumors 2 were positive, and none were negative. No P53 positivity was observed in a 4x3 cm tumor which was P53 negative. This totaled 44 positive and 6 negative cases. The Chi squared test yielded a p value of 0.4016 indicating no statistically significant association between tumor size and P53 IHC status.

DISCUSSION

Gallbladder carcinoma (GBC) is a rare yet aggressive cancer often diagnosed late, leading to high mortality rates. Histopathological evaluation is vital for diagnosis, staging, and treatment planning. Molecular markers like P 53 and HER-2/neu are crucial in understanding GBC's pathogenesis, offering potential for targeted therapies to improve patient outcomes.

In our study, 8 males and 31 females had stones, while 3 males and 8 females did not, totaling 39 with stones and 11 without. The Chi squared test showed no significant association (p value 0.9474). This aligns with Kaur et al. (2020), who reported 12 males and 40 females with stones, and 5 males and 10 without (p value 0.952), and Fukumura et al. (2022), with 15 males and 38 females with stones and 4 males and 12 without (p-value 0.960) . In our tumor site study, 2 males and 6 females had tumors in the Body, and 9

males and 33 females in the Fundus, yielding no significant association (p-value 1.0). Grau et al. (2004) and Fukumura et al. (2022) similarly found no association. For age distribution, our study showed males with a mean age of 60.09 years and females 54.87 years, consistent with findings by Walvir et al. (2024) and Fukumura et al. (2022), who reported similar age distributions [14,15,16,17].

In our study age distribution by P53 IHC status showed 12 P53 positive and 3 P53 negative patients under 50, and 32 positive and 3 negative patients aged 50 and above, with no significant association (p-value = 1.0), consistent with findings by Grau et al. (2004) and Singh et al. (2016). Similarly, sex distribution revealed no significant association between sex and P53 status (p-value = 1.0), aligning with Grau et al. (2004) and Singh et al. (2016). Stone presence and tumor site distribution by P53 status also showed no significant associations, supported by similar results from Kaur et al. (2020), Grau et al. (2004), and Singh et al. (2016) [14,16,18].

In our study on tumor size distribution by P53 IHC status no significant association was found (p-value = 0.4016) similar to findings by Singh et al. (2016) and Ghosh et al. (2013). For histological type 43 adenocarcinoma patients were P53 positive and 6 negative, with no significant association (p-value = 1.0), consistent with Ghosh et al. (2013) and Grau et al. (2004). Histological grade showed a significant association with P53 status (p-value = 0.04), aligning with Ghosh et al. (2013) and Kaur et al. (2020). LVI distribution revealed no significant association (p-value = 0.8847), as also observed by Bora et al. (2023) and Grau et al. (2004) [14, 16, 18, 19, 20].

In our study on PNI distribution by P53 IHC status, 3 patients with PNI were P53 positive, and 41 without PNI were P53 positive, with no significant association (p-value = 1.0). This aligns with findings by Kaur et al. (2020) and Bora et al. (2023). In regional lymph node assessment, 44 patients were P53 positive, with no significant association (p-value = 0.2375), consistent with Singh et al. (2016) and Kaur et al. (2020). pTNM staging also showed no significant association (p-value = 0.0919), similar to Singh et al. (2016) and Ghosh et al. (2013). Age distribution by HER2NEU status showed no significant association (p-value = 0.3681) consistent with Roa et al. (2014) and Jain et al. (2020) [14, 18, 19, 20, 21, 22].

In our study on age distribution by HER2NEU IHC status, 42 patients were HER2NEU positive and 8 negative with no significant association (p value = 0.3681) consistent with Roa et al. (2014) and Jain et al. (2020). For sex distribution, 42 were HER2NEU positive and 8 negative with no significant association (p value = 0.8087) similar to Roa et al. (2014) and Mani et al. (2023). Stone presence also showed no significant association (p value = 0.8087) aligning with Grau et al. (2004) and Abeer et al. (2021). Tumor site distribution revealed no significant association (p-value = 1.0), consistent with findings by Roa et al. (2014) and Jain et al. (2020) [16, 21, 22, 23, 24]

In our study, tumor size distribution by HER2NEU IHC status showed a significant association (p-value = 0.0151), consistent with Jain et al. (2020) and Abeer et al. (2021), who also reported significant associations. Histological type distribution revealed no significant association (p-value = 1.0), similar to findings by Mondal et al. (2017) and Roa et al. (2014). Histological grade distribution showed a significant association (p-value = 0.0042), aligning with Roa et al. (2014) and Abeer et al. (2021). Lymphovascular invasion (LVI) also showed a significant association (p-value = 0.0288), consistent with Abeer et al. (2021) and Grau et al. (2004). Perineural invasion (PNI) distribution showed no significant association (p-value = 0.9741), in line with Abeer et al. (2021) and Mondal et al. (2017) [16, 21, 24, 25].

In our study on regional lymph nodes by HER2NEU IHC status, 42 patients who could not be assessed were HER2NEU positive, and 7 were negative, with no significant association (p-value = 0.3488). This aligns with findings by Mondal et al. (2017) and Abeer et al. (2021). In pTNM staging, our study found 42 HER2NEU positive and 8 negative cases, with no significant association (p-value = 0.1742), consistent with Grau et al. (2004) and Jain et al. (2020), who also reported no significant association between pTNM staging and HER2NEU status with similar p-values [16,22,24,25].

CONCLUSION

This study offers an in depth analysis of the histopathological characteristics and immunohistochemical expression of p53 and HER2NEU in gallbladder carcinoma, highlighting their significant role in the disease's pathogenesis and progression due to their high expression levels in these tumors.

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How to cite: Saakshi Garg, Mahendra Singh. Role of Immunohistochemical Expression of P-53 and HER-2-NEU in Understanding the Pathogenesis and Prognosis of Gall Bladder Carcinoma, *International Medicine,* 2024; 10 (2) :1-8