International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 14, No. 5, May 2025 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_14.5.2025.47

ORIGINAL RESEARCH

Assessment of clinico-pathological relevance of expression of PD-L1 in carcinoma gall bladder

Dr. Vikram Singh Sodha[1], Dr. Hemant Jain[2], Dr. Manisha Kala[3], Dr. Rekha Shekhawat[4]

[1]Assistant Professor, Department of Surgical Gastroenterology, Geetanjali Medical College, Udaipur, Rajasthan, India
[2]Assistant Professor, Ananta Institute of Medical Sciences and Research Centre, Rajsamand, Rajasthan, India
[3]Assistant Professor, Department of Obstetrics & Gynecology, Ananta Institute of Medical Sciences and Research Centre, Rajsamand, Rajasthan, India
[4]Assistant Professor, Department of Community Medicine, SKGMC Sikar, India

Corresponding author
Dr. Rekha Shekhawat
Assistant Professor, Department of Community Medicine, SKGMC Sikar, India
Email: vikramrekhasingh2014@gmail.com

Received: 30 March, 2025 Accepted: 29 April, 2025 Published: 08 May, 2025

ABSTRACT

Background: Present prospective observational study was planned to find out clinico-pathological relevance of expression of PD-L1 in carcinoma Gall Bladder**. Materials & methods:** After obtaining institutional ethical clearance, this observational study was conducted in the department of surgical gastroenterology, KGMU Lucknow. A total of 68 patients of gall bladder carcinoma (resectable, unresectable, metastatic, and incidental) proven by histopathology were prospectively recruited from February 2020 to December 2021. Patients, between 18 to 70 years age and those had been given informed consent were included in the study. Patient with ECOG 3 and 4 were excluded.Information of worked up 68 patients of GBC were retrieved from a prospectively collected computerized data system. Data such as age, gender, comorbidities, symptoms, clinical examinations (general physical and per abdominal), routine blood investigations (CBC, LFT, KFT, PT INR), USG abdomen, tumor markers (CEA & CA 19-9), CECT abdomen & chest, details of surgical procedures, endoscopic interventions, radiological interventions, and histopathological analysis of surgical specimen and trucut biopsy were collected.Hematoxylin and eosin-stained slides of GBC were reviewed by pathologist. Primary outcome was percentage of PD-L1 expression in Gallbladder carcinoma. Criteria for positive immunohistochemical staining was based onTumor Proportion Score (TPS).It was assessed as percentage positive PD-L1. Descriptive statistics was analyzed with SPSS version 17.0 software **Results:** Association of PD-L1 expression with clinico and histopathological variables was seen. At a cut off 10% PD-L1 expression was found significantly associated with absence of ascites (p=0.005), presence of diabetes mellitus (p=0.000) and adjacent organ involvement (p= 0.000). Adenocarcinoma histological type (p=.005) and high TIL density (p=.000) also found significantly associated. At a cut off 1% significant association were found between PD-L1 expression and pathological (III & IVB) and TNM (T2 & T3) staging. **Conclusion:** The results from present study are providing rationale to further explore more evidence so that it may help in better understanding of GBC pathogenesis, in developing better techniques like uniform scoring system/ criteria to identify these molecular abnormalities and in advancement in management paradigm for better survival of gallbladder cancer patients.

Key words: PD-L1, Carcinoma, Gall bladder

INTRODUCTION

Gall bladder cancer (GBC) is the most common cancer of the biliary tract, representing 80%−95% of biliary tract cancers worldwide [(1)]. About 10% of the gallbladder cancer cases are contributed from India. According to GLOBOCON 2020, in India, GBC ranked 20th amongst all cancers, with the number of new cases being 19570 and 5-year prevalence rate of 1.82 per 100,000 population[(2)].

Various risk factors are found to be associated with gall bladder cancer like advanced age, female sex, gallstones, acute inflammation, chronic cholecystitis, xanthogranulomatous cholecystitis, family history, ethnicity, porcelain gallbladder, gallbladder polyps, primary sclerosing cholangitis, choledochal cyst, infection of Salmonella Typhi, S. Paratyphi, and Haemophilus Bilis, parasitic infections, smoking, obesity, anomalous pancreatico-biliary ductal junction

DOI: 10.69605/ijlbpr_14.5.2025.47

(APBDJ) [3-9]. Apart these genetic factors (p53 and K-ras point mutation) also play an important role in widely different frequency of gallbladder cancer worldwide [10, 11].

The USG abdomen has low sensitivity for early gall bladder cancer detection, Triple phase Computed tomography (CT) abdomen is performed to confirmation of diagnosis, assessment of resectability and staging [12].

Due to its rapid progression and dismal prognosis, an urgent need of early diagnosis and surgical resection are required. But, at the time of surgery less than 10% of patients have resectable tumours [13]. Moreover, for resectable tumors five-year survival rates are only 30%–50% and for unresectable cases it is less than 5% [14]. The port-site recurrences also have been reported after laparoscopic cholecystectomies in up to 17% of unsuspected gallbladder cancer cases [15].

In advanced disease (non-regional lymph node/distant metastases, and vascular invasion) only combination chemotherapy is the current standard of treatment in patients who can tolerate cytotoxic chemotherapy [16]. Although, the median overall survival is reported very less with palliative chemotherapy [17].

In recent years molecular profiling has highlighted its importance in various cancers. The several clinical trials have been conducting in GBC to explore effective targeted therapies like HER2, EGFR, VEGFR, PD-1/ PDL-1, TP53, KIT, CDKN2A/B, PI3K)/AKT/ mammalian target of rapamycin (mTOR), and RAS/BRAF/MEK/MAK [18] but still no biomarkers have been validated and entered in clinical practice.

PD-L1 (B7-H1 or CD274) is a membrane-associated protein and specifically binds to PD-1 expressed on T cells and inhibiting their function[19]. There are few effective literatures is available till time about PD-L1overexpression and their clinicopathological association regarding gall bladder carcinoma specially from India where this malignancy is commoner.

Therefore, for a better understanding of the pathological molecular mechanisms of gall bladder carcinogenesis to improve diagnosis, prognosis, and for developing novel targeted therapies for patients with advanced GBC, present prospective observational study was planned to find out clinico-pathological relevance of expression of PD-L1 in carcinoma Gall Bladder**.**

METHODOLOGY

Patients

After obtaining institutional ethical clearance, this observational study was conducted in the department of surgical gastroenterology, KGMU Lucknow. A total of 68 patients of gall bladder carcinoma(resectable, unresectable, metastatic, and incidental) proven by histopathology were prospectively recruited from February 2020 to December 2021. Patients, between 18 to 70 years age and those had been given informed consent were included in the study. Patient with ECOG 3 and 4 were excluded.

Data Collection

Information of worked up 68 patients of GBC were retrieved from a prospectively collected computerized data system. Data such as age, gender, comorbidities, symptoms, clinical examinations (general physical and per abdominal), routine blood investigations (CBC, LFT, KFT, PT INR), USG abdomen, tumor markers (CEA & CA 19-9), CECT abdomen & chest, details of surgical procedures, endoscopic interventions, radiological interventions, and histopathological analysis of surgical specimen and trucut biopsy were collected.

Histopathological &Immunohistochemical analysis

Hematoxylin and eosin-stained slides of GBC were reviewed by pathologist. Tumors site, tumors size, pattern of growth, level of invasion, nodal metastasis, TNM stage and morphological parameters (i.e. nuclear grade, mitosis, necrosis, LVI and PNI) were analyzed.

Immunohistochemical analysis of PDL-1 was performed using the Ventana PDL-1 clone SP263 monoclonal primary antibody on the fully automated Ventana BenchMark XT system.

Outcome

Primary outcome was percentage of PD-L1 expression in Gallbladder carcinoma. Criteria for positive immunohistochemical staining was based onTumor Proportion Score (TPS).It was assessed as percentage positive PD-L1.

PD-L1 TPS < 1% negative

PD-L1 TPS ≥ 1% positive

Secondary outcome measures were proportion of gall bladder carcinoma, different variable wise like age, gender, comorbidities, histological analysis, resectability, CECT finding, TNM staging, treatment modalities.

Statistical Analysis

Descriptive statistics was analyzed with SPSS version 17.0 software. Continuous Variables were presented as mean ± SD. Categorical variables were expressed as Frequencies and percentages. The Pearson's chi-square test or the chi-square test of Association was used to determine if there was a relationship between two categorical Variables. $P<0.05$ was considered statistically significant.

RESULT

The present study included 68 patients; those had a histological diagnosis of gall bladder carcinoma. The mean age was 50 year (49.99± 11.72) and majority were females (72.1%). Gall stone was present in 49 patients (72.06%) and abdominal pain (85.3%) was the most common complaints. Fourty three (63.2%) patients had resectable tumor. Mostly patients had

DOI: 10.69605/ijlbpr_14.5.2025.47

diffuse growth pattern (46.9%), adenocarcinoma (98.5%), poorly differentiated (45.6%) and primary site carcinoma (88.2%). Fourty four (64.7%) patients had tumor size more than 25 mm and 33 (48.5%) had moderate nuclear grading. Mostly patients (33, 48.5%) were belonged to T2 and in Stage II (18, 26.5%). Vascular invasion and perineural invasion were present in 14.7% and 41.2% patients respectively. Table 1 shows details of treatment modalities. Extended cholecystectomy was the most common procedure.

Table 1

Treatment Modalities	No of patients	Percentage (%)
Extended cholecystectomy	33	48.5
Extended cholecystectomy with CBD excision with RYHJ	6	8.8
Completion extended cholecystectomy	4	5.9
Palliative surgery (GJ + FJ)	3	4.4
USG guided biopsy, ERCP CBD stenting	3	4.4
USG guided PTBD with biopsy	11	16.2
USG guided biopsy	8	11.8
Total	68	100

PD-L1 expression was found positive in 14 (20.6%) and 2 (2.9%) patients at a cut off 1% and ≥10% respectively. **Table 2**and **Table 3** depict association of PD-L1 expression with clinico and histopathological variables. At a cut off 10% PD-L1 expression was found significantly associated with absence of ascites (p=0.005), presence of diabetes mellitus (p=0.000) and adjacent organ involvement (p= 0.000). Adenocarcinoma histological type (p=.005) and high TIL density (p=.000) also found significantly associated.
At a cut off 1% significant association were found between PD-L1 expression and pathological (III & IVB) and TNM (T2& T3) staging.

Table 2
Association of PD-L1 expression and clinicopathological variables

Variables	PD-L1 expression at 1% cut-off		P value	PD-L1 expression at ≥ 10% cut-off		P value
	Positive (%) N=14	Negative (%) N=54		Positive (%) N=2	Negative (%) N=66	
Age						
<60Year	11(78.6%)	41(76.0%)	0.884	2(100.0%)	50(75.8%)	0.960
>60Year	3 (21.4%)	13(24.0%)		0	16(24.2%)	
Gender						
Male	4 (28.6%)	15(27.8%)	0.783	1 (50.0%)	18(27.3%)	0.925
Female	10(71.4%)	39(72.2%)		1 (50.0%)	48(72.7%)	
Resectability						
Resectable	10(71.4%)	33(61.1%)	0.894	0	43(65.15%)	0.163
Unresectable	0	11(20.4%)		1 (50.0%)	10(15.15%)	
Metastatic	4 (28.6%)	10(18.5%)		1 (50.0%)	13(19.70%)	
CA 19-9						
≥40U/l	12(85.7%)	44(81.5%)	0.982	2 (100%)	54 (81.8%)	0.782
<40U/L	2 (14.3%)	10 (18.5%)		0	12 (18.2%)	
CEA						
≥5µg/l	5 (35.7%)	26(48.15%)	0.595	2 (100%)	29 (43.9%)	0.397
<5ug/l	9 (64.3%)	28(51.85%)		0	37 (56.1%)	
HTN						
Present	0	4 (7.4%)	0.680	0	4 (6.1%)	0.243
Absent	14 (100%)	50 (92.6%)		2 (100%)	62 (93.9%)	
DM						
Present	1 (7.1%)	3 (55.6%)	0.680	2 (100%)	2 (3.0%)	0.000
Absent	13(92.9%)	51(44.4%)		0	64 (97%)	
Gall stones						
Present	10(71.4%)	39 (72.2%)	0.783	0	49 (74.2%)	0.132
Absent	4 (28.6%)	15 (27.8%)		2 (100%)	17 (25.8%)	

DOI: 10.69605/ijlbpr_14.5.2025.47

Vascular invasion						
Present	0	10 (18.5%)	0.187	1 (50%)	9 (13.6%)	0.677
Absent	14 (100%)	44 (81.5%)		1 (50%)	57 (86.4%)	
IAC lymph node involvement						
Present	2 (14.3%)	3 (5.6%)	0.589	1 (50%)	4 (6.1%)	0.332
Absent	12(85.7%)	51 (94.4%)		1 (50%)	62 (93.9%)	
Perineural invasion						
Present	8 (57.1%)	20 (37.0%)	0.290	2 (100%)	26 (39.4%)	0.324
Absent	6 (42.9%)	34(63%)		0	40 (60.6%)	
Nodal metastasis						
Present	8 (57.1%)	24 (44.4%)	0.584	2 (100%)	30 (45.5%)	0.422
Absent	6 (42.9%)	30 (55.6%)		0	36 (54.5%)	
Liver metastasis						
Present	3 (21.4%)	7 (13.0%)	0.709	2 (100%)	10 (15.1%)	0.677
Absent	11(78.6%)	47(87%)		0	56 (84.9%)	
Adjacent organ involvement						
CBD (9)	2 (14.3%)	7 (13.0%)	0.305	0	9 (13.6%)	0.000
Duodenum (3)	0	3 (55.5%)		2 (100%)	1 (1.5%)	
Liver (8)	1 (7.1%)	7 (13.0%)		0	8 (12.1%)	
Multiple organs (9)	0	9 (16.7%)		0	9 (13.6%)	
Chemotherapy						
Received	0	2 (3.7%)	0.876	0	2 (3.0%)	0.061
Not received	14 (100%)	52 (96.3%)		2 (100%)	64 (97%)	
Necrosis						
Present	6 (42.9%)	26 (48.2%)	0.958	2(100.0%)	30 (45.5%)	0.422
Absent	8 (57.1%)	28(51.8%)		0	36 (54.5%)	
Lymphovascular emboli						
Present	8 (57.1%)	20 (37.0%)	0.290	2 (100%)	26 (39.4%)	0.324
Absent	6 (42.9%)	34 (63%)		0	40 (60.6%)	
Lymphadenopathy						
Present	5 (35.7%)	19 (35.2%)	0.782	2 (100%)	22 (33.3%)	0.233
Absent	9 (64.3%)	35 (64.8%)		0	44 (66.7%)	
Ascites						
Present	0	1 (1.8%)	0.464	0	1 (1.5%)	0.005
Absent	14 (100%)	55 (98.2%)		2 (100%)	65(99.5%)	

Table 3: Association of PD-L1 expression and Histopathological variables

Variables (No of patients)	PD-L1 expression at 1% cut-off		P value	PD-L1 expression at ≥ 10% cut-off		P value
	Positive (%) N=14	Negative (%) N=54		Positive (%) N=2	Negative (%) N=66	
Tumor Site						
Primary	14 (100%)	46 (85.2%)	0.286	2 (100%)	58 (87.9%)	0.555
Metastatic	0	8 (14.8%)		0	8 (12.1%)	
Tumor Size						
<25 mm	5 (35.7%)	19 (35.2%	0.782	0	24 (36.4%)	0.757
>25 mm	9 (64.3%)	35 (64.8%)		2 (100%)	42 (63.6%)	
Tumor mass						
Mass	12(85.7%)	54(100.0%)	0.053	2(100.0%)	62(93.94%)	0.243
No residual mass	2 (14.3%)	0		0	4 (6.06%)	
Growth Pattern (64)						
Diffuse	6 (42.8%)	24 (48%)	0.234	2 (100%)	28 (45.2%)	0.689
Polypoidal	6 (42.8%)	9 (18%)		0	15 (24.2%)	
Infiltrative	2 (14.4%)	11 (22%)		0	13 (20.9%)	
Ulceroproliferative	0	6 (12%)		0	6 (9.7%)	
Tumor location (64)						
Body	1 (8.3%)	2 (3.8%)	0.869	0	3 (4.8%)	0.650
Neck	2 (16.7%)	10 (19.2%)		0	12 (19.4%)	

DOI: 10.69605/ijlbpr_14.5.2025.47

Fundus	1 (8.3%)	4 (7.7%)		0	5 (8.0%)	
Body & Neck	2 (16.7%)	5 (9.6%)		0	7 (11.3%)	
Fundus & Body	4 (33.3%)	11 (21.2%)		0	15 (24.2%)	
Whole gallbladder	2 (16.7%)	20 (38.5%)		2 (100%)	20 (32.3%)	
Histological type						
Adenocarcinoma	14(100.0%)	53 (98.1%)	0.464	2 (100%)	65 (98.5%)	0.005
Papillary carcinoma	0	1 (1.9%)		0	1 (1.5%)	
Histological grade						
Well-differentiated	0	13 (24.0%)	0.000	0	13 (19.7%)	0.292
Moderate-differentiated	13 (92.9%)	11 (20.4%)		0	24 (36.4%)	
Poor-differentiated	1 (7.1%)	30 (55.6%)		2 (100%)	29 (43.9%)	
Nuclear grading						
Mild	0	17 (31.5%)	0.042	0	17 (25.8%)	0.057
Moderate	10 (71.4%)	23 (42.6%)		0	33 (50%)	
Severe	4 (28.6%)	14 (25.9%)		2 (100%)	16 (24.2%)	
No. of Mitosis						
<10/HPF	9 (65.3%)	21 (38.9%)	0.160	0	30 (45.5%)	0.580
>10/HPF	5 (35.7%)	33 (61.1%)		2 (100%)	36 (54.5%)	
TIL density						
Low	13 (92.9%)	50 (92.6%)	0.589	0	63 (95.5%)	0.000
High	1 (7.1%)	4 (7.4%)		2 (100%)	3 (4.5%)	
Staging of Tumor						
I	0	2 (3.7%)	0.010	0	2 (3.0%)	0.830
II	0	18 (33.3%)		0	18 (27.3%)	
IIIA	6 (42.9%)	5 (9.3%)		0	11 (16.7%)	
IIIB	4 (28.6%)	5 (9.3%)		0	9 (13.6%)	
IVA	0	12 (22.2%)		1 (50%)	11 (16.7%)	
IVB	4 (28.6%)	12 (22.2%)		1 (50%)	15 (22.7%)	
TNM staging						
T1	6 (42.9%)	26 (48.2%)	0.019	0	2 (3.0%)	0.578
T2	8 (57.1%)	28(51.8%)		0	34 (51.5%)	
T3	8 (57.1%)	20 (37.0%)		1 (50%)	20 (30.3%)	
T4	6 (42.9%)	34 (63%)		1 (50%)	10 (15.2%)	

DISCUSSION

The carcinoma of gallbladder is a very aggressive form of biliary tract cancers (BTC) because it has atypical presentation at earlier stage, incidental diagnosis, and poor prognosis. Currently radical surgeries for resectable and conventional chemotherapy for unresectable cases are potential strategies to treat gallbladder carcinoma. However additional therapeutic strategies included targeted therapies have been continuously explored since 1988 [20] based on blocking, specific molecular targets that are responsible for tumor cell proliferation and antitumor immune responses. The aberrant expressions of PD-L1 have been reported in patients of multiple cancers including gallbladder cancer [21,22].

In this light, present prospective observational study was conducted on 68 patients of carcinoma gall bladder with aim of evaluation of PDL-1 expression in tumor cells with their clinico-histopathological relevance, so that this subgroup of patients can be benefitted with special molecular targeted therapy.

The current literature is limited regarding PDL-1 expression & its clinicopathological association in gallbladder carcinoma. Till date only four studies have been conducted in Asia and India on the distribution of PD-L1 expression in GBC. The present study observed that out of 68 patients of GBC; PDL-1 expression was found positive in 14 (20.6%) and 2 (2.9%) patients at a cut off 1% and ≥10% respectively.

Neyaz A et al[23] study found PDL-1 expression in 23% of tumor cells. Kim JH et al[22] and Lin et al[21] studies correspondingly reported somewhat lower tumor cell positivity at a cut off 1%, in approximately 18% of the patients, which is more in line with the frequency determined by Albrecht T et al[25] study i.e. 14.7%.

At a higher cut off, Kim JH et al reported PDL-1 expression in 13.8% patients with a cutoff level of 10%, and 7.9% patients with a cutoff level of 50%, it was corresponding with Neyaz et al study, where 14.9% of the patients demonstrating a high tumoral expression of at least 10% cutoff. While in Albrecht T et al study at higher cut-offs of 10% and 25%, expression was found lower (4.7% and 3.1%, respectively), which is quite similar with present study.

The inconsistency in results of different studies may be due to use of different cut off levels (e.g., 1%, 5%, 25%, and 50%), antibody clones (e.g., SP263, SP142,

DOI: 10.69605/ijlbpr_14.5.2025.47

22C3, 22-8, and E1L3N clones) and immunohistochemistry methods. The difference in ethnicity and environment between Western and Eastern GBC cohorts may also be a contributor for this discrepancy.

The present study observed a significant association of PDL-1 expression at 1% cut off with histological grade (p=0.000), nuclear grade (p=0.042), pathological staging (p=0.010) and T staging (p=0.019). Higher expression was observed in moderate (92.9%) and poorly differentiated (7.1%) tumor, in moderate (71.4%) and severe (28.6%) nuclear grading, in stage III A (42.9%), III B (28.6%) and IV B (28.6%), in T 3 (64.3%) and T2 stage (35.7%).

Whereas, at a cut off 10% PDL-1 expression was significantly associated with histological type (p=0.005), diabetes mellitus (p=0.000), ascites (p=0.005), adjacent organ involvement (p= 0.000) and TIL density (p= 0.000). The expression was present in cases of adenocarcinoma and high TIL density.

Kim JH et al concluded that PDL-1 expression at any cutoff was significantly correlated with poorer differentiation and the presence of lymphovascular invasion. While with cutoff levels of 10% and 50%, it was associated with presence of perineural invasion, higher T category, and higher pathologic stage. In addition, PD-L1 expression with 1% and 10% cutoff levels was correlated with larger tumor size.

Lin et al did not found significant correlation of PDL-1 expression with any clinicobiological or pathological parameters except for higher CD8+ TIL density.

In Neyaz et al study, at TPS ≥ 1, an increase in PD-L1 expression was significantly seen in squamous and adenosquamous cell carcinoma, from well-differentiated adenocarcinoma to poorly differentiated adenocarcinoma, from low density to high density of TILs, from low nuclear grade to higher nuclear grade, from low mitotic activity to high mitotic activity, from no lymph node metastasis to lymph node metastasis and from lower stage to higher stage.

Albrecht T et al study concluded significant association with poor tumor differentiation only. There was no significant correlation observed with any other clinico-pathological parameters.

From the findings of present study and other studies, it can be suggested that PD-L1 expression is associated with poor prognostic factors. Likewise, some studies, which were done on different tumor types, also observed that tumors with poor differentiation, vascular invasion, nodal metastasis, higher stage, adenocarcinoma histology, and lower survival rate were correlated with higher PDL1 expression [23, 24].

Present study evaluated somewhat lower but noteworthy proportion of PDL-1 positive GBC cases in which targeted therapy may improve the prognosis of patients. PDL-1 expression was observed more in poorly differentiated and in advanced stage GBC, it suggests that controlled clinical trials of PDL-1 targeted therapy can be conducted in patients with advanced gallbladder cancer. The results from present study are providing rationale to further explore more evidence so that it may help in better understanding of GBC pathogenesis, in developing better techniques like uniform scoring system/ criteria to identify these molecular abnormalities and in advancement in management paradigm for better survival of gallbladder cancer patients.

Recommendation: There should be a uniform criterion for evaluation of PD-L1 expression in gall bladder cancers on similar lines as breast cancer and larger clinical trials should be conducted to find the potential of PDL-1 based targeted therapy in GBC

Limitations of study: study had small sample size and used only immunohistochemistry for evaluation of expression.

REFERENCES

1. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol. 2014;6:99-109.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249
3. Mahantshetty UM, Palled SR, Engineer R, Homkar G, Shrivastava SK, Shukla PJ. Adjuvant radiation therapy in gall bladder cancers: 10 years experience at Tata Memorial Hospital. J Cancer Res Ther. 2006;2(2):52-56.
4. Benson AB, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. J Natl Compr Canc Netw. 2009;7(4):350-391.
5. Rawla P, Sunkara T, Thandra KC, Barsouk A. Epidemiology of gallbladder cancer. Clin Exp Hepatol. 2019;5(2):93-102.
6. Matsukura N, Yokomuro S, Yamada S, Tajiri T, Sundo T, Hadama T, Kamiya S, Naito Z, Fox JG. Association between Helicobacter bilis in bile and biliary tract malignancies: H. bilis in bile from Japanese and Thai patients with benign and malignant diseases in the biliary tract. Jpn J Cancer Res. 2002;93(7):842-847.
7. Unisa S, Jagannath P, Dhir V, Khandelwal C, Sarangi L, Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. HPB (Oxford). 2011;13(2):117-125.
8. Dutta U, Poornachandra KS. Gallbladder polyps: how to pick up the sinister ones. J Gastroenterol Hepatol. 2009;24(2):175-178.
9. Hickman L, Contreras C. Gallbladder Cancer: Diagnosis, Surgical Management, and Adjuvant Therapies. Surg Clin North Am. 2019;99(2):337-355.
10. Dutta U, Nagi B, Garg PK, Sinha SK, Singh K, Tandon RK. Patients with gallstones develop gallbladder cancer at an earlier age. Eur J Cancer Prev. 2005;14(4):381-385.

DOI: 10.69605/ijlbpr_14.5.2025.47

11. Dutta U. Gallbladder cancer: can newer insights improve the outcome? J Gastroenterol Hepatol. 2012;27(4):642-653.
12. Kalra N, Suri S, Gupta R, Natarajan SK, Khandelwal N, Wig JD, Joshi K. MDCT in the staging of gallbladder carcinoma. AJR Am J Roentgenol. 2006;186(3):758-762.
13. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol. 2000;95(6):1402-1410.
14. Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist. 2010;15(2):168-181.
15. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. J Gastrointest Surg. 2007;11(5):671-681.
16. Sirohi B, Singh A, Jagannath P, Shrikhande SV. Chemotherapy and targeted therapy for gall bladder cancer. Indian J Surg Oncol. 2014;5(2):134-141.
17. Canale M, Monti M, Rapposelli IG, Ulivi P, Sullo FG, Bartolini G, et al. Molecular Targets and Emerging Therapies for Advanced Gallbladder Cancer. Cancers (Basel). 2021;13(22):5671.
18. Song X, Hu Y, Li Y, Shao R, Liu F, Liu Y. Overview of current targeted therapy in gallbladder cancer. Signal Transduct Target Ther. 2020;5(1):230.
19. Boussiotis VA. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. N Engl J Med. 2016;375(18):1767-1778.
20. Brodsky FM. Monoclonal antibodies as magic bullets. Pharm Res. 1988;5(1):1-9.
21. Lin J, Long J, Wan X, Chen J, Bai Y, Wang A, et al. Classification of gallbladder cancer by assessment of $CD8^+$ TIL and PD-L1 expression. BMC Cancer. 2018;18(1):766.
22. Kim JH, Kim K, Kim M, Kim YM, Suh JH, Cha HJ, et al. Programmed death-ligand 1 expression and its correlation with clinicopathological parameters in gallbladder cancer. J Pathol Transl Med. 2020;54(2):154-164.
23. Neyaz A, Husain N, Kumari S, Gupta S, Shukla S, Arshad S, et al. Clinical relevance of PD-L1 expression in gallbladder cancer: a potential target for therapy. Histopathology. 2018;73(4):622-633.
24. Mody K, Starr J, Saul M, Poorman K, Weinberg BA, Salem ME, et al. Patterns and genomic correlates of PD-L1 expression in patients with biliary tract cancers. J Gastrointest Oncol. 2019;10(6):1099-1109.
25. Albrecht T, Brinkmann F, Albrecht M, Lonsdorf AS, Mehrabi A, Hoffmann K, et al. Programmed Death Ligand-1 (PD-L1) Is an Independent Negative Prognosticator in Western-World Gallbladder Cancer. Cancers (Basel). 2021;13(7):1682.