BCL-2 Expression and Histopathological Staging of Renal Cell Carcinoma in a Tertiary Care Setting Hospital

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Abstract

Background: *Renal cell carcinoma (RCC) represents the commonest form of kidney cancer, constituting approximately 90% of all diagnosed kidney cancer. Patients with over expression of BCL-2 in renal cell carcinoma have a poorer prognosis. BCL-2 expression in RCC may assist in the targeted therapies and improve patient management.*

Aim: *To evaluate the expression of BCL-2 in histomorphologically diagnosed renal cell carcinoma and its association with histopathological stage (pT).*

Methods: *This cross-sectional study was conducted in the Department of Pathology, Dhaka Medical College, Dhaka, from March 2021 to February 2023 among purposively included 60 histomorphologically diagnosed RCC patients. Immunostaining with BCL-2 antibody was also done and findings were recorded. Statistical analysis was carried out using the SPSS software version 25.*

Results: *A total of 26 (43.3%) patients were in pT2 stage, 24 (40.0%) patients belonged to pT1 stage and the remaining 10 (16.7%) patients were in pT3 stage. Positive expression of BCL-2 was detected in 37 (61.7%) cases while 23 (38.3%) patients had negative BCL-2 expression. BCL-2 expression was significantly associated with pT stage (p=0.035).*

Conclusion: *BCL-2 immunomarker, combined with histopathological staging can identify individuals at high risk for kidney cancer. BCL-2 expression is crucial for patients with cancer that does not respond to chemotherapy.*

Keywords: *Renal Cell Carcinoma, BCL-2 Expression, Histopathological Staging.*

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Introduction

Renal cell carcinoma accounts for 1-3% of all cancers in humans and represents 75-80% of kidney cancer cases in adults.[1] RCC originates from renal stem cells primarily found in the proximal nephron and tubular epithelium.[2]

Risk factors for renal cell cancer include tobacco smoking, prolong use or misuse of certain pain medications, obesity, hypertension, family history of renal cell cancer, genetic history or hereditary papillary renal cancer.[3]

BCL-2 is significant for comprehending the progression and prognosis of renal cell carcinoma (RCC). The B cell leukemia/ lymphoma 2 gene (BCL-2) is classified as a proto-oncogene. It is found on chromosome 18q21.33. This gene was initially identified by cloning the breakpoint region of the t (14;18) translocation, a chromosomal abnormality typically associated with follicular lymphomas.[4] Unlike many oncogenes, BCL-2 does not induce cell division but instead promotes cell survival by inhibiting apoptosis.[5]

Several studies show that elevated BCL-2 expression correlate with various clinical factors, such as the tumor stage, size, and its

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metastatic spread. This implies that BCL-2 could aid in forecasting patient outcomes. Increased BCL-2 expression are associated with more advanced stages of renal cell carcinoma (RCC), indicating a potentially more aggressive cancer. The BCL-2 expression is linked to tumor progression.[6] Sometimes, BCL-2 expression correlates with poorer survival outcomes.[7]

Elevated BCL-2 expression, in conjunction with larger tumor size are significant risk factors for recurrence of the disease and mortality in patients.[8] Typically, BCL-2 expression are more pronounced in aneuploid tumors, which might suggest a more aggressive cancer type; however, its precise role in prognosis remains uncertain.[9]

Though BCL-2 expression is frequently observed in RCC, its effectiveness as predictor is limited. This indicates a need for further investigation to enhance the understanding of its significance in clinical environments.[7] This study was conducted to assess the expression of BCL-2 in histomorphologically diagnosed renal cell carcinoma and its association with histopathological stage (pT).

Materials and Methods

This was a part of large cross-sectional study carried out from the period March 2021 to February 2023 in the Department of Pathology, Dhaka Medical College, Dhaka. The objective was to assess BCL-2 expression and its association with staging in renal cell carcinoma. By purposive sampling technique total 60 histomorphologically diagnosed renal cell carcinoma patients of any age and sex were included in this study. Informed written consent was taken from each participant after describing the purpose and procedure of the study. Data was collected by face-to-face interviewing and reviewing medical records. Immunostaining for BCL-2 were done on all the 60 cases at Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Histopathological stage was categorized in two groups: 1) Low stage: pT1 and pT2, 2) High Stage: pT3 and pT4. After thorough checking and coding statistical analyses were carried out using Statistical Package for the Social Science (SPSS) version 25. Categorical variables were presented as frequencies and percentages, numerical variables were presented as mean and standard deviation. Chi-square and Fisher Exact tests were used to analyze association between categorical variables. Statistical significance was set as 95% confidence level. Results having p-values <0.05 were considered as statistically significant. Ethics was maintained strictly at every point of this study. Ethical clearance was obtained from Ethical Review Committee (ERC) of DMC.

Results

This study was carried out among 60 histopathologically diagnosed cases of renal cell carcinoma to assess expression of BCL-2 and its association with staging in renal cell carcinoma.

Table-I described that mean (±SD) age was 57.2 (±11.7) years. Smoking was found in majority 66.7% of the patients as risk factors. Maximum 83.3% patient (n=50) underwent radical nephrectomy. A total of 58.3% cases (n=35) RCC were located in upper pole of kidney.

Table-I

Distribution of patients according to baseline characteristics (n=60)

Attributes	Frequency (n)	Percentage (%)
Age (Years)		
24-44	06	10
45-64	35	58.3
65-75	19	31.7
Mean (±SD) =57.2 (±11.7)		
Risk factors (multiple response)		
Smoking	40	66.7
Hypertension	37	61.7
Obesity	34	56.7
Type of specimen		
Partial	10	16.7
Radical	50	83.3
Location of RCC		
Upper	35	58.3
Lower	25	41.7

Table-II

Distribution of patients according to histopathological staging (pT) of renal cell carcinoma and BCL-2 expression (n=60).

Attributes	Frequency (n)	Percentage (%)
Staging		
pT1	24	40
pT2	26	43.3
pT3	10	16.7
BCL-2 expression		
Positive	37	61.7
Negative	23	38.3

Majority 43.3% of patients (n=26) belonged to pT2 stage followed by 40% (n=24) in pT1 stage and remaining 16.7% patients (n=10) were in pT3 stage of RCC. BCL-2 expression was detected positive in 61.7% patients (n=37) while 38.3% patients (n=23) showed negative BCL-2 expression (Table-II).

Table-III

Association between histopathological staging and BCL-2 expression (n=60)

Staging (pT)	BCL-2 expression		p-value
	Positive	Negative	
pT1 & pT2	34 (68%)	16 (32%)	0.035
pT3	3 (30%)	7 (70%)	

Among the patients who were in pT1 & pT2 stage, 68% patients (n=34) were detected as positive expression of BCL-2 and 32% cases (n=16) showed negative expression. About 70% patients (n=7) were detected as negative expression and 30% cases (n=3) showed positivity of pT3 stage. Staging of RCC was statistically associated with BCL-2 expression ($p<0.05$) stated in Table-III.

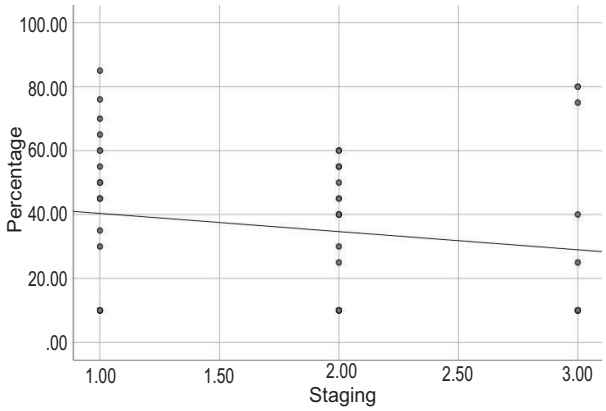

Fig 1 : *Scatter diagram showing association between histopathological staging and percentages of BCL-2 expression (n=60)*

Figure 1 showed that there was significant negative correlation between histopathological staging and percentages of BCL-2 expression.

Discussion

The current study revealed 58.3% RCC patients were in age range of 45-64 years. Smoking was found in majority 66.7% of the patients followed by hypertension in 61.7% and obesity in 56.7% of patients as risk factors for RCC. Tobacco smoking has been linked to many common cancers including RCC. A variety of carcinogens associated with the pathogenesis of RCC are present in tobacco smoke. There is epidemiological evidence supporting a causal association with tobacco, including a dose-response relationship between risk and daily cigarette consumption and a decline in risk with more years of smoking cessation.[10] Similarly another study confirmed that obesity was significantly associated with RCC risk (BMI e" 35 vs. < 25 kg/m2).[11] Another study also found strong smoking history (71%) and (58%) RCC patients were hypertensive.[12]

There are different types of surgery like partial nephrectomy, radical nephrectomy which involves taking out the kidney, the adrenal gland, nearby tissue, and usually the nearby lymph nodes as well.[3] The present study stated that maximum 83.3% patients (n=50) underwent radical nephrectomy and remaining 16.7% patients (n=10) went for partial nephrectomy. Regarding location of renal cell

carcinoma (RCC) in majority 58.3% cases (n=35) RCC were located in upper pole of kidney and in remaining 41.7% cases (n=25) RCC were located in lower pole.

In the present study, it was detected that 43.3% patients were in pT2 stage, 40.0% patients belonged to pT1 stage and the remaining 16.7% patients were in pT3 stage. A similar study reported 34.2% cases were in pT1 stage, 28.5% patients in pT2 stage and 34.2% cases in pT3 stage.[13] Moreover Girgin et al. (2022) also found 44 cases in pT1 stage, 27.4% cases in pT3 stage followed by 27.4% patients in pT4 stage.[14]

High expression of BCL-2 prevents cell proliferation, suppresses tumor growth and thereby is associated with a lower pT stage in RCCs, as previously stated.[7] It was additionally detected in the current study that BCL-2 expression was significantly associated with stage in a statistically significant level ($p<0.05$). Therefore, BCL-2 expression might be applied as a novel predictor of better prognosis in RCC patients.[7]

In this study, BCL-2 expression was inversely associated with pT stage. In pT1 and pT2 stage, 34 (68.0%) were detected with positive expression and 16 (32.0%) showed negative expression. Again, in pT3 stage, 3 (30.0%) cases showed positive expression and 7 (70.0%) showed negative expression. A study found a significant inverse relationship between BCL-2 expression and pT stage of RCCs.[15] A possible explanation to this might be based on the suggested anti proliferative role of BCL-2 protein.[7,16]

Studies showed that BCL-2 was more frequently detected in tumors with pT stage.[17] Contrary to inferential belief that BCL-2 as anti-apoptotic gene would promote cell cycle, Pierce et al. (2002) found that the expression of the protein interferes with the cell cycle progression.[16] It has also been proposed that by increasing cell survival, BCL-2 may facilitate differentiation and that loss of expression is related to loss of differentiation and neoplastic progression.[18]

According to the present study, RCC with low stage (pT1 and pT2) demonstrates higher expression of BCL-2. But it does not reveal any significant association with histopathological types of RCC. Therefore, it could be hypothesized that high expression of BCL-2 prevents cell proliferation, suppresses tumor growth and thereby is associated with a lower pT stage in RCCs. This study might open a new avenue for the clinical evaluation of BCL-2 to provide a therapeutic benefit for the treatment of RCC patients.

There were some limitations. Firstly, specimens were gathered exclusively from DMCH. Collecting specimens from various centers across the country would provide more comprehensive information. Secondly, patient follow-up was not conducted. Finally, it was not feasible to make remarks on the patients' outcomes.

Conclusion

BCL-2 immunomarker along with histopathological staging can help to diagnose individuals at high risk for kidney cancer. BCL-2 may also have therapeutic uses. It may help to determine cancers especially those are chemotherapy resistant.

Declarations

Ethics approval and consent to participate

Before data collection, both verbal and written informed consent was taken from patients.

Consent for publication

All authors have approved this manuscript for publication.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MA, MN, and MH participated in the design of the study, data interpretation and drafted the manuscript. MA, MN, MFH, and MH contributed to the data design, data interpretation and data analysis. SSS, SA, and MFH did the critical review of the manuscript.

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