Original Article

Immunoexpression of E-Cadherin And Its Association With Histological Type and Grade of Renal Cell Carcinoma

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ABSTRACT

Introduction: Renal cell carcinoma (RCC) is one of the most common cancers worldwide. Its aggressiveness and behavior depend on different histopathological parameters, including histological types, stages, grades, etc. **Objective**: This study aims to observe the immunohistochemical expression of E-cadherin in renal cell carcinoma and compare it with different histopathological parameters. **Methodology**: This cross-sectional observational study was conducted in the Department of Pathology, Shaheed Suhrawardy Medical College, Dhaka, Bangladesh, from March 2021 to February 2023. In this study, 50 diagnosed cases of renal cell carcinoma were included. Paraffin blocks from all cases were collected, and sections were taken from each block for routine hematoxylin and eosin (H&E) staining, as well as immunohistochemical staining for the E-cadherin antibody. Relevant clinical and microscopic data, including age, sex, tumor size, histomorphologic type, and tumor grade, were collected and recorded in a predesigned data collection sheet. The statistical analysis used the spss version 26 for Windows (SPSS Inc., Chicago, Illinois, USA). The Fisher Exact test was used to analyze the association between different categorical variables. **Results**: 50 patients diagnosed with renal cell carcinoma were selected for the study. In this study, the age of the patients varied from 20-75 years. Most cases were in the age group 40-59 years (78%), and the mean age of the study cases was 50.86 ± 9.55 (SD) years. About 70% (n=35) of the patients were male. Most were clear cell carcinoma 29 (58%). Among the 50 cases, 20 (40%) patients were at stage pT1. Stage pT2 comprised 24 (48%) cases. Stage pT3 were found in 5 (10%) cases and stage pT4 in 1 (2%) case. Among the 50 cases, 30 (60%) patients were grade 2, grade 1 comprised 9 (18%) cases, grade 3 were found in 6 (12%) cases and grade 4 in 5 (10%) cases. E-cadherin expression was preserved in 28 (56%) cases. Statistical analysis revealed a significant association of E-cadherin with pathological staging (pT) and histological grades. However, morphological variants did not show any significant association with E-cadherin staining. **Conclusion**: E-cadherin expression was preserved in 56% cases of renal cell carcinoma. Loss of E-cadherin expression was significantly associated with advanced histological grades and stages of renal cell carcinoma.

Key words: E-cadherin, Renal cell carcinoma, Metastasis

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Background

Kidney cancer is the 14th most common form of cancer worldwide with an estimated 431,288 new cases diagnosed and about 179,368 deaths worldwide in 2020 (IARC, 2020).[1] Renal cell carcinoma accounts for 85% of all primary malignant renal tumors in adults. The prevalence of Renal cell carcinoma in Bangladesh is 1.96%.[1] Renal cell carcinoma (RCC) originated from the renal epithelium. The disease consists of more than ten histological and molecular subtypes, of which clear cell RCC (CCRCC) is the most common. Most of the detected renal cell carcinomas are small tumors, advanced, or harbor distant metastases at diagnosis.[2] To date, tumor stage and nuclear grade were considered the most important prognostic variables for patients with RCC. However, in many cases, they are insufficient to predict the clinical behavior of these tumors. No specific serum markers or prognostic factors are available to predict the development of metastases or tumor recurrence or to observe the response to therapy. E-cadherin is a transmembrane calcium-dependent protein involved in cell-to-cell adhesion.[3] A reduction or loss in expression of E-cadherin is considered to elicit detachment of tumor cells from primary lesions and correlated with distant metastasis as well as higher tumor grade and stage.[4]

Renal cell carcinoma usually metastasizes widely in the early stage through hematogenous route, and the clinical outcome of patients with the same tumor grade may vary significantly. In cancer, E-cadherin function is disrupted through various mechanisms, such as inactivating somatic and germline mutations, epigenetic silencing by DNA methylation and epithelial-to-mesenchymal transition (EMT)-inducing transcription factors, as well as dysregulated protein processing.[5] Loss of E-cadherin expression is associated with tumor invasion and metastasis. As molecular alteration precedes phenotypic change, the immunohistochemical study is a valuable tool for identifying aggressive cancers. To date, few studies have explored the predictive role of E-cadherin in renal cell carcinoma. The rationale of this study is to observe the immunohistochemical expression of E-cadherin in renal cell carcinoma, evaluate their association with histological type and grade, and determine the usefulness of E-cadherin immunostains as an adjunctive tool.

Materials and method

This study was a cross-sectional observational study. Place of study was the Department of Pathology, Shaheed Suhrawardy Medical College, Dhaka, Bangladesh. Cases histologically diagnosed as renal cell carcinoma at the Department of Pathology, ShSMC, and NIKDU were included in this study. Specimens were collected from all age groups and both sexes. The study was carried out from March 2021 to February 2023. Purposive sampling was done. Histologically diagnosed cases of renal cell carcinoma in patients of any age and sex were included in the study. Patients having a history of receiving radiotherapy or chemotherapy before surgery were excluded from the study. A total of 50 cases were taken as a study sample. During the collection of specimens, patients' information and demographic data were recorded systematically in a prepared proforma. Informed written consent was obtained from the patient's attendant in each case. All the cases were numbered chronologically, and the same number was given to histological and immunohistochemical slides. After obtaining permission from the Ethical Review Committee (ERC) of ShSMC, each specimen was collected in 10% buffered formalin. In the pathology laboratory, specimens were grossed according to the standard protocol, followed by tissue processing, paraffin embedding, sectioning of the paraffin blocks, and H&E staining. Cases and histological parameters were evaluated elaborately, including morphological type, pathological stage, and tumor grade. Representative sections from each paraffin block were selected for immunohistochemical stain with E-cadherin. Formalin-fixed paraffin-embedded tissue sections of 3-4 micrometer thickness were used. The primary Antibody was FLEX Monoclonal Mouse Anti-Human E-cadherin Clone NCH-38, Ready to use. DAKO REALTM EnVision TM (HRP RABBIT/MOUSE) (ENV) was used as secondary Antibody. E-Cadherin staining in the cells of normal breast tissue from a mastectomy specimen served as a positive control. Evaluation of immunostaining and scoring were performed by light microscopy. The staining intensity and pattern were evaluated on a scale of 0 to 3 and classified as follows:

1. **Preserved:** complete circumferential membrane staining of E-cadherin with high intensity in >90% of tumor cells: score 3
2. **Heterogeneous membranous:** <90% positive tumor cells: score 2
3. **Cytoplasmic:** no membranous staining and only cytoplasmic staining: score 1
4. **Absent:** Absence of staining: score 0

First group: Preserved (with the score 3)

Second group: Negative (with scores 2, 1, and 0).[6]

The statistical analysis was conducted using the Statistical Package for Social Sciences version 26 for Windows (SPSS Inc., Chicago, Illinois, USA) Fisher Exact test and Chi-square tests to analyze the association between different categorical variables.

Observations and Results

Table 1 shows that out of the total 50 cases, 39(78%) cases belonged to the age group of 40-59 years. 70%(n=35) patients were male. Clear cell carcinoma 29(58%) cases. 20(40%) patients were at stage pT1. Stage pT2 comprised 24(48%) cases and Stage pT3 5(10%) cases. 30(60%) patients were Grade 2. Grade 1 comprised 9(18%) cases. Grade 3 was found in 6(12%) cases and grade 4 in 5(10%) cases. E-Cadherin expression was mostly preserved 28(56%) among all the patients of the present study. E-cadherin expression was negative in 22(44%) cases.

Table 1: Distribution of patients according to age, gender, morphological variants, tumor stage, tumor grade, and E-cadherin expression (n=50).

Age (years)	Frequency	(%)
20-39	3	6
40-59	39	78
≥60	8	16
	Mean ± SD	50.86 ± 9.55
Gender		
Male	35	70
Female	15	30
Morphological variants		
Clear RCC	29	58
Papillary RCC	13	26
Chromophobe carcinoma	7	14
Collecting duct carcinoma	1	2
Tumor stage		
pT1	20	40
pT2	24	48
pT3	5	10
pT4	1	2
Tumor grade		
Grade 1	9	18
Grade 2	30	60
Grade 3	6	12
Grade 4	5	10
E-cadherin expression		
Preserved	28	56
Negative (Heterogenous membranous and cytoplasmic)	22	44

Table 2 shows that no significant association was observed between E-Cadherin expression and tumor morphology (n=50). It also shows that in the T1 and T2 stages, 13 (65%) and 15 (62.5%) E-Cadherin expressions were mostly preserved, while in T3 and T4, none of the patients showed preserved E-Cadherin expression. Fisher's exact test showed a significant statistical difference between the stage of tumor and E-Cadherin expression (p=0.023). In this table, E-cadherin expression was mostly preserved in grade 1 and grade 2, with 8(88.9%) and 18(60%) cases, respectively. In grade 3, 2 (33.3%) cases showed preserved E-cadherin expression, whereas in grade 4, none of the patients showed preserved E-cadherin expression. Fisher's exact test showed a significant statistical difference between grade of tumor and E-Cadherin expression (p=0.006).

Table 2: Association of E-Cadherin expression with morphological variants (n=50), stage and grade of clear cell carcinoma (n=29).

Morphological variants (N=50)	Preserved	Negative	p-value
Clear cell RCC	14 (48.3%)	15 (51.7%)	
Papillary RCC	10 (76.9%)	3 (23.1%)	0.251ns
Chromophobe	3 (42.9%)	4 (57.1%)	
Collecting duct carcinoma	1 (100.0%)	0 (0.0%)	
Stage	Preserved	Negative	
pT1	13 (65.0%)	7 (35.0%)	
pT2	15 (62.5%)	9 (37.5%)	0.023s
pT3	0 (0.0%)	5 (100.0%)	
pT4	0 (0.0%)	1 (100.0%)	
Grade	Preserved	Negative	
Grade 1	8 (88.9%)	1 (11.1%)	
Grade 2	18 (60.0%)	12 (40.0%)	0.006s
Grade 3	2 (33.3%)	4 (66.7%)	
Grade 4	0 (0.0%)	5 (100.0%)	

ns = not significant s = significant *p value was determined by Fisher's Exact test.

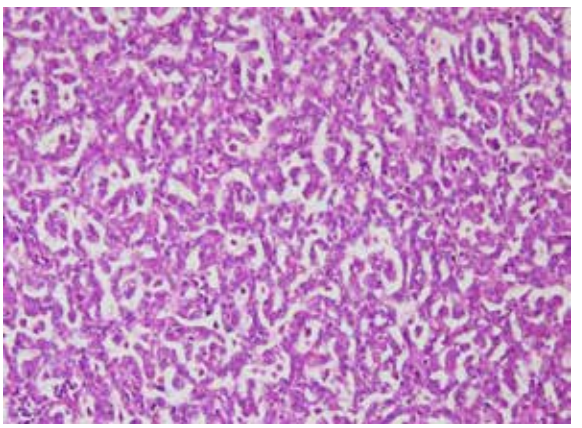

Figure 1(A): Photomicrograph showing Papillary RCC (G-1) (H&E X100).

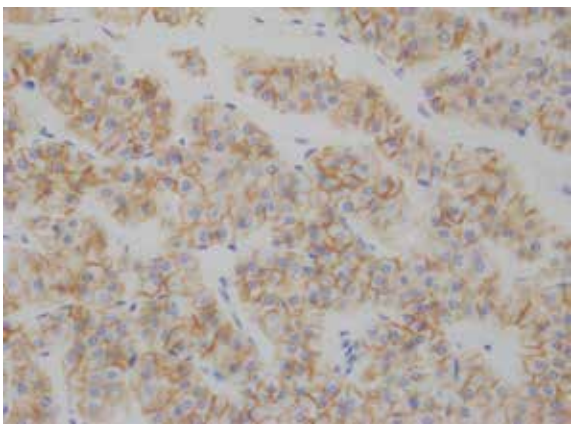

Figure1(B): Photomicrograph showing Papillary (G-1) with preserved E- Cadherin expression (IHC X200).

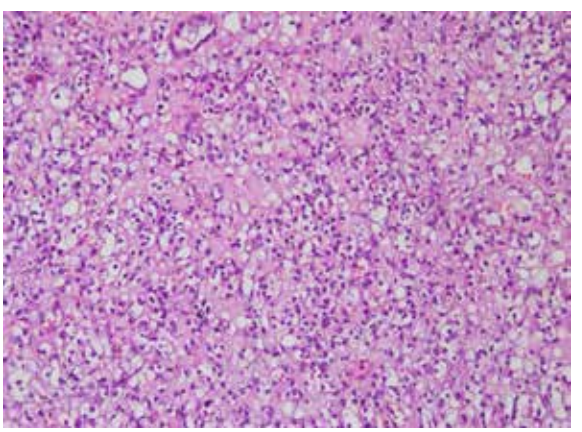

Figure 2(A): Photomicrograph showing Clear Cell RCC (G-2) (H&E X200).

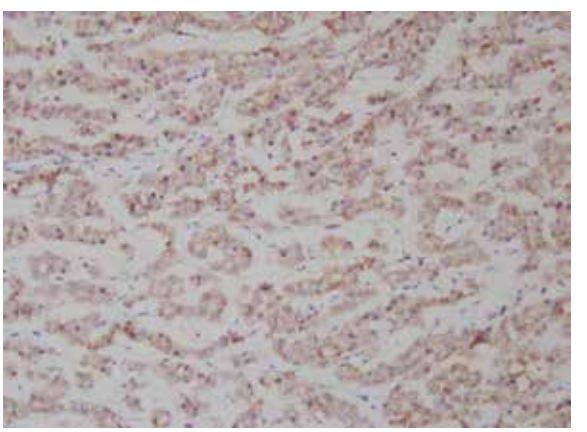

Figure 2(B): Photomicrograph showing Clear Cell RCC (G-2) with preserved E- Cadherin expression (IHC X200).

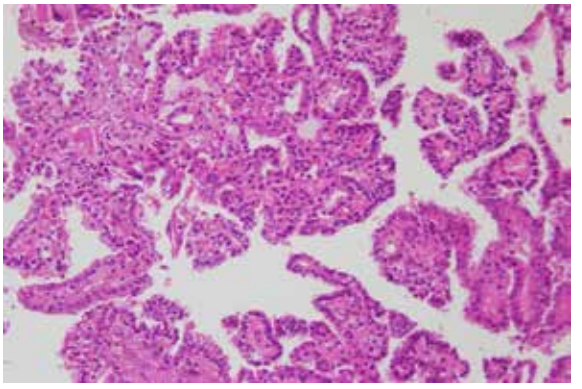

Figure 3(A): Photomicrograph showing Papillary RCC (G-3) (H&E X200).

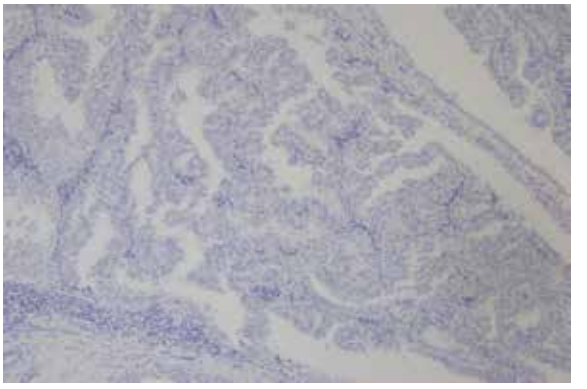

Figure 3(B): Photomicrograph Papillary RCC (G-3) with negative E-Cadherin expression (IHC X100).

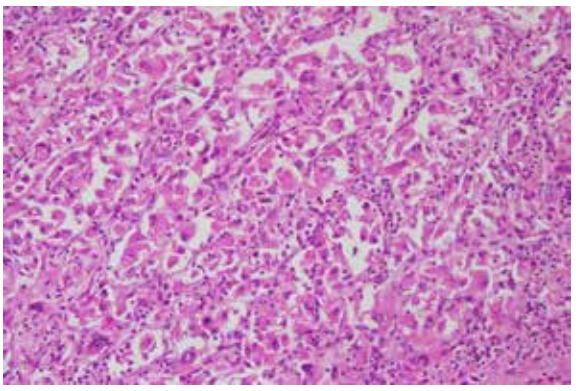

Figure 4(A): Photomicrograph showing Chromophobe RCC (G-4) (H & E X200).

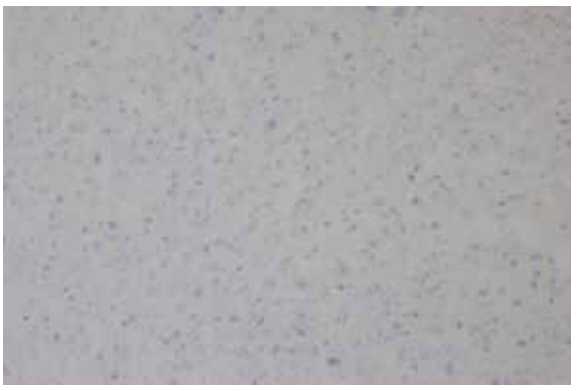

Figure 4 (B): Photomicrograph showing Chromophobe RCC (G-4) with negative E-Cadherin expression (IHC X200).

Discussion

In this study, the total number of cases was 50 nephrectomy specimens histologically diagnosed with renal cell carcinoma. Statistical analysis showed that the mean age of the cases was 50.86 ± 9.55 (SD) years (Table 1). The majority of 39(78%) cases were in the age group 40-59 years. According to this study, 35 (70%) of the cases were male, and 15 (30%) were female, with a male-to-female ratio of 2.3:1 (Table 1). Most of the tumors were clear cell carcinoma 29 (58 %). The second most common papillary renal cell carcinoma was 13(26%) followed by chromophobe variant 7(14 %) and collecting duct carcinoma 1(2%) (Table 1). The E-cadherin expression was evaluated by immunohistochemistry in 50 cases in this study. Out of the 50 cases, E-Cadherin expression was preserved in 28(56%) cases. E-cadherin expression was negative in 22(44%) cases. Negative patterns include heterogeneous membranous, cytoplasmic, and absent staining. The present study finding also correlated with a study conducted by Harb et al. (2018) at Zagazia university of Egypt, where positive E-cadherin expression was detected in 27(38.5%) out of all 70 cases.[7]

The association between morphological variants of renal cell carcinoma and expression of E-cadherin was not significant in this study. This finding was similar to that of Hanna et al. (2010), who found no association between E-cadherin immunostaining and histological subtypes (Table 2). Statistical analysis revealed a significant association of E-cadherin expression with pathological staging (pT) of renal cell carcinoma (Table 2). E-cadherin expression was lost in the higher stage of the tumor. A similar study conducted at Nigata university, Japan by Katagiri et al. (1995) also showed absence of E-cadherin expression was correlated with the higher pathological stages (stage 3 or 4).[8] Similar result was found also in a study conducted by Burandt et al.(2021).[9] After statistical analysis, the association between E-cadherin expression and the grade of the tumor was statistically significant ($p < 0.05$) (Table 2). E-cadherin expression was

progressively lost in the higher grade of the tumors. It was correlated with Harb et al. (2018), which revealed a statistically significant association of loss of E-cadherin expression with higher grades of tumors.[7] Other studies by Andreiana et al. (2019) and Langner et al. (2004) showed a similar result in which all grade 3 and most grade 2 tumors lost E-cadherin expression. [10,11]

Conclusion

In conclusion, the loss of E-cadherin expression is significantly correlated with advanced histological grade (G) and stage (pT) of renal cell carcinoma. The use of E-cadherin immunomarkers, in combination with histological parameters, may provide valuable prognostic information for identifying high-risk renal cell carcinoma patients with metastatic potential.

Limitations

Our study had several limitations. First, the sample size of our study was limited because it was a single-center study. Next, our follow-up data were incomplete.

Recommendations

Larger sample size, longer durations, multi-center studies with reliable, reproducible, and equivalent standardized techniques, and use of other biomarkers and molecular studies would produce more precise, representative data.

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