Immunohistochemical Expression of Extracellular Matrix Metalloproteinase Inducer (EMMPRIN/CD147) in Renal Cell Carcinoma and Its Association with Histological Grade and Pathological Stage

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Abstract

Background: Renal cell carcinoma (RCC) is the commonest malignant epithelial tumor of kidney. Histological grade and stage are major prognostic indicators; however, additional biomarkers may improve prognostic assessment. EMMPRIN/CD14 is associated with tumor invasion, angiogenesis, and metastasis. The aim of this study is to evaluate immunohistochemical expression of EMMPRIN/CD147 in RCC and determine its association with histological grade and pathological stage.

Methods: This cross-sectional study included 40 nephrectomy specimens diagnosed as RCC. Histological grading was done according to WHO/ISUP system and staging by AJCC TNM classification. Immunohistochemical staining for EMMPRIN/CD147 was performed and scored by intensity and proportion of stained cells.

Results: Clear cell RCC was the commonest subtype (67.5%). High EMMPRIN expression was observed in 27 (67.5%) cases. Strong membranous and cytoplasmic positivity was more frequent in higher grade and advanced stage tumors. Significant association was found between EMMPRIN expression and histological grade and pathological stage ($p<0.05$).

Conclusion: EMMPRIN/CD147 high expression is associated with aggressive behavior of RCC and may be a useful prognostic biomarker.

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Introduction

Renal cell carcinoma (RCC) is the most common malignant epithelial neoplasm of the kidney and accounts for approximately 85–90% of adult renal malignancies worldwide. The global incidence of RCC has increased over recent decades, partly due to wider use of cross-sectional imaging and increasing prevalence of obesity, hypertension, and smoking. Men are affected more commonly than women, and most cases occur in the sixth to seventh decades of life.[1]

RCC represents a heterogeneous group of tumors with diverse histomorphology, molecular alterations, and clinical behavior. The 2022 World Health Organization (WHO) Classification of Urinary and Male Genital Tumors introduced important refinements in renal tumor taxonomy, including broader recognition of molecularly defined renal carcinomas. Clear cell RCC remains the most common subtype, followed by papillary and chromophobe RCC.[2,3] Tumor stage and histological grade remain the most important prognostic indicators in RCC. The International Society of Urological Pathology (ISUP) grading system, based primarily on nucleolar prominence, is widely accepted for clear cell and papillary RCC.[4] However, tumors with similar grade and stage may show markedly different biological behavior, indicating the need for additional biomarkers that may improve prognostic stratification.[5] Although surgical resection remains the mainstay of treatment for localized disease, a proportion of patients experience recurrence or develop metastasis after nephrectomy. Advanced RCC has historically shown limited response to conventional chemotherapy and radiotherapy, although targeted agents and immunotherapy have improved outcomes. Biomarkers that identify aggressive disease may assist in surveillance planning and therapeutic decision-making.[1,5]

Extracellular matrix metalloproteinase inducer (EMMPRIN), also known as CD147 or basigin, is a transmembrane glycoprotein belonging to the immunoglobulin superfamily. CD147 contributes to tumor progression by stimulating matrix metalloproteinases, enhancing extracellular matrix degradation, promoting angiogenesis, and facilitating metabolic adaptation through monocarboxylate transporters. Recent reviews indicate that CD147 overexpression is associated with poor prognosis in multiple human malignancies and may represent a therapeutic target.[6–8] In renal neoplasia, studies suggest that increased CD147 expression may correlate with higher tumor grade, advanced stage, and aggressive behavior.[9] In order to maximize patient selection for particular therapy modalities, research into this improved newer prognostic marker should be conducted. However, data from Bangladesh are lacking. Therefore, the present study was undertaken to assess immunohistochemical expression of EMMPRIN/CD147 in renal cell carcinoma and determine its association with histological grade and pathological stage.

Methods

This cross-sectional analytical study was carried out in the Department of Pathology, Mymensingh Medical College, Bangladesh, during the period from July 2022 to June 2024. Histopathologically, diagnosed cases of renal cell carcinoma from nephrectomy specimens were included in the study. A total of 40 cases were selected purposively according to predefined inclusion and exclusion criteria. Cases with adequate formalin-fixed paraffin-embedded tissue blocks and complete clinicopathological data were enrolled. Poorly preserved tissue, insufficient representative tumor tissue, previously treated tumors, and non-RCC renal neoplasms were excluded. Relevant demographic and clinical information

including age, sex, and tumor laterality were collected from pathology records and clinical documents. Gross examination of nephrectomy specimens was performed according to standard pathology protocols. Tumor size, location, capsular involvement, renal sinus extension, necrosis, and adjacent structure involvement were documented.

Representative tissue sections were processed routinely and stained with hematoxylin and eosin. Histological typing was performed according to the WHO 2022 classification.[2,3] Tumors were graded using the ISUP grading system for renal cell carcinoma.[4] Pathological staging was assigned according to the AJCC TNM staging system.[10] For immunohistochemistry, 4–5 µm paraffin sections were mounted on coated slides. Following deparaffinization and rehydration, heat-induced antigen retrieval was performed. Endogenous peroxidase activity was blocked and sections were incubated with primary monoclonal antibody against EMMPRIN/CD147. Secondary antibody and chromogen were subsequently applied, followed by hematoxylin counterstaining. Appropriate positive and negative controls were used. Tumor cell membranous and/or cytoplasmic brown staining was considered positive. Expression was evaluated according to proportion of positive cells and staining intensity. Final immunoreactivity was categorized as negative, weak (+), moderate (++), and strong (+++). For statistical purposes, negative and weak positive cases were grouped as low expression, whereas moderate and strong positive cases were grouped as high expression.

Data were analyzed using SPSS software. Categorical variables were expressed as frequency and percentage. Association between EMMPRIN expression and clinicopathological variables was assessed using Chi-square test or Fisher's exact test where appropriate. A p value <0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Review Board of Mymensingh Medical College before commencement of the study.

Results

This study assessed 40 nephrectomy specimens diagnosed as renal cell carcinoma. Clinicopathological characteristics. Immunohistochemical expression of EMMPRIN/CD147 and their associations with histological grade and pathological stage were evaluated. Table I shows the clinicopathological characteristics of the study population. The majority of patients belonged to the 61–70 years age group (42.5%) with male predominance (67.5%), and clear cell renal cell carcinoma was the most common histological subtype (67.5%).

Table I: Clinicopathological Characteristics of Renal Cell Carcinoma Cases (n=40)

Variables	Number	Percentage (%)
Age group (years)		
≤40	3	7.5
41–50	7	17.5
51–60	10	25.0
61–70	17	42.5
>70	3	7.5
Sex		
Male	27	67.5
Female	13	32.5
Tumor subtype		
Clear cell RCC	27	67.5
Papillary RCC	8	20.0
Chromophobe RCC	5	12.5

Table II demonstrates the distribution of EMMPRIN/CD147 expression among renal cell carcinoma cases. High EMMPRIN expression was observed in 67.5% of cases, whereas low expression was found in 32.5% of cases.

Table II: Final Categorization of EMMPRIN Expression

Category	Number	Percentage (%)
Low expression	13	32.5
High expression	27	67.5

Table III shows the association between EMMPRIN expression and histological grade of renal cell carcinoma. High EMMPRIN expression was significantly more frequent in high-grade tumors compared to low-grade tumors (p=0.012).

Table III. Association of EMMPRIN Expression with Histological Grade

Histological Grade	Low Expression n (%)	High Expression n (%)	p value
Low grade	10 (76.9)	8 (29.6)	
High grade	3 (23.1)	19 (70.4)	0.012*

**Chi-square test applied*

Table IV demonstrates the association between EMMPRIN expression and pathological stage of renal cell carcinoma. Advanced pathological stages (Stage III–IV) showed significantly higher EMMPRIN expression compared to early stages (p=0.028).

Table IV. Association of EMMPRIN Expression with Pathological Stage

Pathological Stage	Low Expression n (%)	High Expression n (%)	p value
Stage I–II	11 (84.6)	14 (51.9)	
Stage III–IV	2 (15.4)	13 (48.1)	0.028*

**Chi-square test applied*

Figure 1 shows moderate EMMPRIN/CD147 immunoexpression in clear cell renal cell carcinoma. Tumor cells exhibit distinct membranous and cytoplasmic brown staining, indicating moderate positivity (++) on immunohistochemistry (IHC ×200).Figure 2 demonstrates strong EMMPRIN/CD147 immunoexpression in grade IV clear cell renal cell carcinoma. Diffuse intense membranous and cytoplasmic staining (+++) is observed in the tumor cells, suggesting marked overexpression of EMMPRIN/CD147 (IHC ×200).

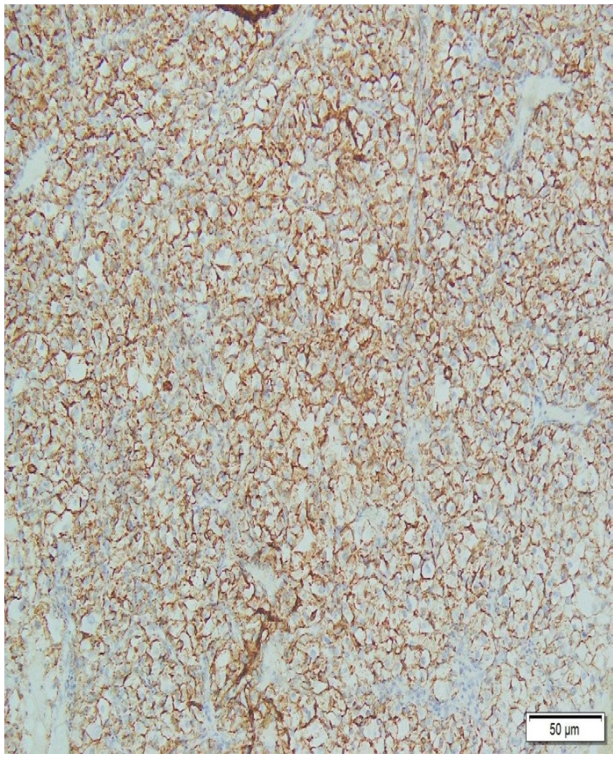

Figure 1. Photomicrograph showing clear cell carcinoma EMMPRIN expression: Moderate positive (++) (IHC x 200)

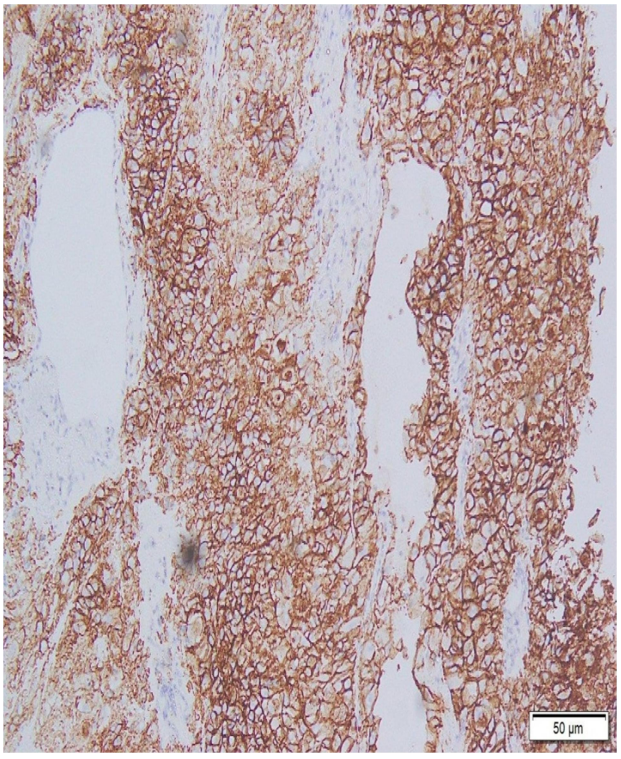

Figure 2. Photomicrograph showing clear cell carcinoma, grade-IV EMMPRIN expression: Strong positive (+++) (IHC x 200)

Discussion

Renal cell carcinoma is characterized by marked clinicopathological and molecular heterogeneity. Conventional prognostic indicators such as stage and grade remain important, but they do not completely explain the variable clinical course seen in patients with morphologically similar tumors. Biomarkers reflecting invasive and metastatic potential may therefore be clinically valuable.[5]In the present study, most patients belonged to the sixth and seventh decades of life with male predominance. These findings are consistent with global epidemiological data showing that RCC is more common in older adults and occurs more frequently in men.[1]

Clear cell RCC was the most common histological subtype in this study. This observation corresponds with the WHO classification and major pathological series reporting clear cell RCC as the predominant subtype, followed by papillary and chromophobe RCC.[23]A substantial proportion of cases in the present study demonstrated high EMMPRIN/CD147 expression. Immunoreactivity was predominantly membranous with variable cytoplasmic staining, which is biologically plausible given that CD147 is a transmembrane glycoprotein. Similar staining patterns have been reported in multiple epithelial malignancies.[6–8]A significant association was observed between high EMMPRIN expression and increasing histological grade. This supports the concept that CD147 overexpression is linked to tumor dedifferentiation and aggressive phenotype. CD147 promotes matrix metalloproteinase production, extracellular matrix remodeling,

and tumor cell invasion, which may contribute to higher-grade morphology.[6–8]
The present study also demonstrated significant association between increased EMMPRIN expression and advanced pathological stage. This is consistent with previous evidence suggesting that CD147 promotes angiogenesis, local invasion, and metastatic dissemination. Experimental and clinical studies have shown that CD147 can modulate VEGF signaling and tumor microenvironment interactions, thereby facilitating tumor progression.[6,7] Studies specifically evaluating RCC have reported that elevated CD147 expression is associated with adverse clinicopathological features and may have prognostic value.[9] In addition, recent literature has explored CD147 as a therapeutic target in oncology, including antibody-based and pathway-directed strategies.[7,8] The practical implication of the present study is that immunohistochemical assessment of EMMPRIN/CD147 may complement routine histopathological reporting in RCC, particularly in identifying tumors with higher aggressive potential. Patients with strong expression may benefit from closer surveillance and future biomarker-driven therapeutic approaches.

However, this study had limitations including relatively small sample size, single-center design, and absence of survival follow-up. Larger multicenter studies with long-term outcome analysis are recommended to validate the prognostic significance of EMMPRIN/CD147 in RCC.

Conclusion

In conclusion, the present study demonstrates that EMMPRIN/CD147 overexpression is significantly associated with higher histological grade and advanced pathological stage in renal cell carcinoma, indicating its potential role as an adverse prognostic biomarker.

Ethical Approval: Obtained from Institutional Review Board, Mymensingh Medical College.

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Conflict of Interest: None declared.

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