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# Histomorphological Subtyping of Renal Cell Carcinoma: Diagnostic Utility of CK7, CAIX, and AMACR

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**Abstract:** ***Background: Histological subtyping of renal cell carcinoma (RCC) is essential because different subtypes have distinct prognostic and therapeutic implications. Morphological overlap often makes diagnosis difficult, necessitating immunohistochemistry (IHC). Objectives: To classify RCC based on histomorphology and evaluate the role of CK7, CAIX, and AMACR in subtype differentiation. Methods: A prospective cross-sectional study was conducted over two years on 40 nephrectomy specimens diagnosed as RCC. Tumors were classified on hematoxylin and eosin sections and graded according to the ISUP grading system. IHC was performed using CK7, CAIX, and AMACR. Statistical analysis was done using SPSS version 26. Results: The mean age was 56.9 ± 13.0 years. Clear cell RCC was the commonest subtype (47.5%), followed by papillary RCC (35%), chromophobe RCC (10%), and clear cell papillary RCC (7.5%). CAIX showed positivity in all clear cell RCCs, while AMACR was positive in all papillary RCCs. CK7 was positive in all chromophobe and clear cell papillary RCCs and in 85.7% of papillary RCCs. The association between histological subtype and marker expression was statistically significant (p<0.001). Conclusion: The combined use of CK7, CAIX, and AMACR accurately differentiates the major RCC subtypes and is a valuable adjunct to routine histopathological evaluation.***

**Keywords:** Renal cell carcinoma, Immunohistochemistry, CK7, CAIX, AMACR.

## 1. Introduction

Renal cell carcinoma (RCC) accounts for nearly 90% of primary renal malignancies and represents one of the most common urological cancers (1). Histological subtype is an important predictor of prognosis and therapeutic response. Although routine histopathology accurately diagnoses most cases, overlapping morphological features between clear cell, papillary, chromophobe, and clear cell papillary RCC may create diagnostic uncertainty. Immunohistochemical markers such as CK7, CAIX, and AMACR improve diagnostic accuracy by demonstrating characteristic expression patterns. This study evaluated the role of these markers in subclassifying RCC.

## 2. Materials and Methods

This prospective cross-sectional study was conducted over two years in the Department of Pathology, Calcutta National Medical College and Hospital, Kolkata.

**Inclusion criteria**
Forty nephrectomy specimens diagnosed as RCC were included who presented with symptoms of hematuria, flank pain and renal mass.

**Exclusion criteria**
Non-neoplastic renal diseases, metastatic tumors, mesenchymal tumors, cystic renal diseases, inadequate biopsies, and previously treated cases.

Routine histopathological examination with hematoxylin and eosin staining was performed, followed by ISUP grading. Immunohistochemistry using CK7, CAIX, and AMACR was carried out in all cases. Statistical analysis was performed using SPSS version 26, and the Chi-square test was used to determine associations. A p-value <0.05 was considered statistically significant.

## 3. Results

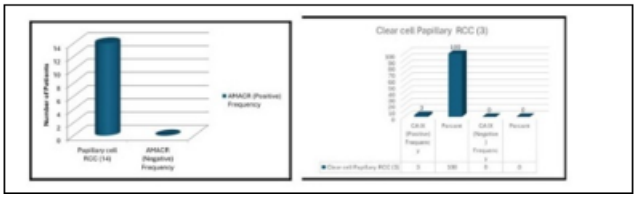
The majority of patients were aged 61–70 years (30%), with a mean age of 56.9 ± 13.0 years. The male-to-female ratio was 1:1.
Among the 40 tumors, 19 (47.5%) were clear cell RCC, 14 (35%) papillary RCC, 4 (10%) chromophobe RCC, and 3 (7.5%) clear cell papillary RCC.

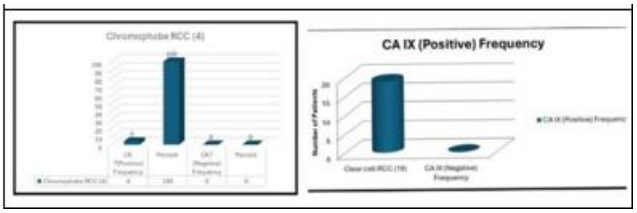
CAIX showed diffuse positivity in all clear cell RCCs and all clear cell papillary RCCs, while all papillary and chromophobe RCCs were negative. AMACR was positive in all papillary RCCs but negative in clear cell papillary and chromophobe RCCs, with focal positivity in three clear cell RCCs. CK7 was positive in all chromophobe RCCs, all clear cell papillary RCCs, and 12 of 14 papillary RCCs, whereas only one clear cell RCC expressed CK7.

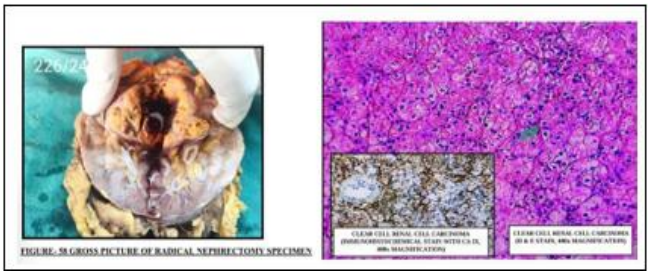
The correlation between histological subtype and CK7, CAIX, and AMACR expression was highly significant (p<0.001).

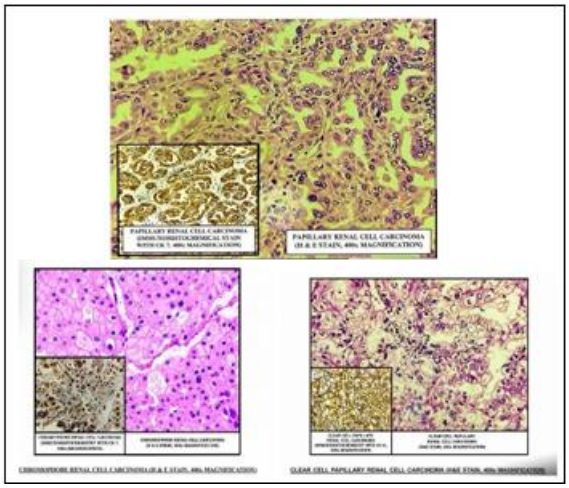
**IHC pattern in different morphological subtypes of RCC**

| Histologic subtypes | CK7 | | CA IX | | AMACR | |
|---|---|---|---|---|---|---|
| | positive | negative | positive | negative | positive | negative |
| Clear cell RCC (n=19) | 1 | 18 | 19 | 0 | 3 | 16 |
| Papillary RCC ( n=14) | 12 | 2 | 0 | 14 | 14 | 0 |
| Clear cell papillary RCC ( n=3) | 3 | 0 | 3 | 0 | 0 | 3 |
| Chromophobe RCC (n=4) | 4 | 0 | 0 | 4 | 0 | 4 |
| | | | | | | |







Kidney cancer is the most lethal malignancy of the urinary tract, according for approximately 3% of adult cancers worldwide, with RCC being the most common subtype. Its incidence is higher in men, increases with age, and shows marked geographical variation, with global age-standardized incidence and mortality rates of 4.4 and 1.8 per 100,000 population, respectively (2-4)

## 4. Discussion

Accurate subclassification of RCC is essential because treatment and prognosis differ among histological subtypes. In the present study, clear cell RCC was the predominant subtype, consistent with previous reports. Diffuse CAIX positivity was highly characteristic of clear cell RCC, whereas AMACR showed diffuse expression in papillary RCC. CK7 expression was predominantly observed in papillary, chromophobe, and clear cell papillary RCC.

These findings are consistent with published studies by Al-Ahmadie et al. (5), Williamson et al. (6), Rao et al. (7) and Kim et al. (8), demonstrating that a limited IHC panel significantly improves diagnostic accuracy in RCC with overlapping morphology.

## 5. Conclusion

Histopathological examination remains the primary diagnostic modality for RCC. However, the combined use of CK7, CAIX, and AMACR provides reliable subclassification of RCC, particularly in morphologically challenging cases. This three-marker panel offers a practical and cost-effective diagnostic approach in routine pathology practice. Since our study was single institution base, and the number of cases were small, it was not possible to give a generalized result to comment on the whole population. The present study may be reviewed as a component of a large multicentric study to reach a definite conclusion.

As the study period is short, survival analysis over a longer period couldnot be done in the short time limit.

The main weakness of IHC approaches were limited technical reproducibility, subjective interpretation, and qualitative readouts although all the IHC was performed and interpreted in a single laboratory by same core group of pathologist to avoid these issues as much as possible.

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