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Evaluation of N-cadherin Expression in Renal Cell Carcinoma

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الملخص:

مقدمة: يتم تشخيص سرطان الخلايا الكلوية (ار سي سي) بشكل متكرر، وهو أكثر أنواع سرطان المسالك البولية المميتة، ويصعب التنبؤ به من خلال المعايير السريرية المرضية العادية. تم التعرف على العديد من المؤشرات الحيوية وهي قيد البحث للتأكد من فعاليتها.

الهدف: هدفت هذه الدراسة إلى تقييم ظهور ان-كاديرين في أنواع مختلفة من سرطان الخلايا الكلوية (ار سي سي) وعلاقته بالمعايير السريرية المرضية وتقييم أهميته التنبؤية، وبقاء المرضي علي قيد الحياة .

المواد وطريقة الدراسة: اشتملت هذه الدراسة على سلسلة متتالية من 48 من مرضى سرطان الخلايا الكلوية، تم جمعها من المرضى الذين خضعوا لاستئصال الكلية الجذري أو الجزئي مع بياناتهم السريرية المرضية والمتابعة. تم تقييم ظهور ان-كاديرين عن طريق الكيمياء المناعية في مصفوفة الأنسجة الدقيقة. تم تصنيف ظهور ان-كاديرين لغرض التحليل الإحصائي، وتم تنفيذ علاقة الارتباط مع المتغيرات السريرية المرضية باستخدام الإصدار 22 من الحزمة الإحصائية للعلوم الاجتماعية 22 (اس بي اس اس). استخدمت طريقة كابلان ماير لتحليل البقاء على قيد الحياة .

النتائج: تم ظهور ان-كاديرين بدرجة عالية في (85.4٪) من حالات سرطان الخلايا الكلوية. (77.4٪) من نوع الخلية الصافية وجميع حالات الحليمي، والكروموفوب، ومجرى التجميع، والمتغير الساركوماتويد من سرطان الخلايا الكلوية. كان نمط ظهور ان-كاديرين غير طبيعي (السيتوبلازم وخليط من الغشاء والسيتوبلازم). كان هناك فرق كبير في البقاء على قيد الحياة بين حالات التعبير العالي غير الطبيعي والتعبير المنخفض عن ظهور ان-كاديرين بقيمة معنوية= (0.01). ولم يكن هناك ارتباط بين ظهور ان-كاديرين وعوامل المرضى السريرية وخصائص الورم ونتائج المرضى وتكرار ظهورالورم.

الاستنتاج: ظهور التعبير العالي غير الطبيعي ان-كاديرين يعتبر علامة تنبؤية جيدة.

الكلمات المفتاحية:

سرطان الخلايا الكلوية، ان-كاديرين، الصبغة الهستوكيميائية المناعية، تنبؤ.

Abstract

Introduction: Renal cell carcinoma (RCC) is frequently diagnosed as the most lethal urological cancer and is difficult to predict by ordinary clinicopatho¬logical parameters. Several prognostic biomarkers have been recognized and they are under investigation.

Aim: This study aimed to assess the expression of N-cadherin in different types of RCC, its clinicopathological associations, patients` survival and prognostic inference.

Materials and Methods: This study included a consecutive series of 48 RCC collected from patients who underwent radical or partial nephrectomy with their clinicopathological and follow-up data. N-cadherin expression was evaluated by immunohistochemistry using a tissue microarray. Marker expression was categorized for statistical analysis, the correlations with clinicopathological variables carried out using SPSS version 22. The Kaplan-Meier method was used for survival analysis.

Results: N-cadherin was highly expressed in 85.4% of RCC cases; 77.4% of clear cell type and all cases of papillary, chromophobe, collecting duct, and sarcomatoid change RCC. The expression pattern was abnormal (cytoplasmic or mixed membranous and cytoplasmic). There was a significant difference in the survival between the cases of abnormal high expression and low expression of N-cadherin (P=0.01). There were no associations between N-cadherin expression and the patients' factors, tumor characteristics, the patients' outcomes and tumor recurrence.

Conclusion: An abnormal high expression of N-cadherin is a better prognostic factor.

Keywords: Immunohistochemistry; N-cadherin; Renal cell carcinoma; Prognosis.

1. INTRODUCTION

Globally, renal cell carcinoma (RCC) represents one of the commonly diagnosed cancers. It is the sixth most diagnosed cancer in men (5%) and the tenth in women (3%). RCC remains one of the most lethal urological malignancies and the 13th common cause of cancer deaths in the world. [1] The prognosis of patients with RCC is difficult to predict by clinicopatho¬logical parameters as the neoplastic cells have the potential to metastasize depending on their biological features. Therefore, the

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biological markers including the protein expression are important to predict tumor behavior, improving treatment and patient prognosis.[2] Cadherins are transmembrane glycoproteins that play a role in the development of different organs, and in tumorigenesis and metastasis. N-cadherin promotes cell motility when expressed by epithelial cancer cells such as breast, prostate, urinary system and pancreatic cancers through genetic reprogramming; a process known as epithelial-to-mesenchymal transition (EMT). Failure of expression of epithelial cadherin (E-cadherin) takes place with either up-regulation or new synthesis and expression of neural cadherin (N-cadherin), the feature associated with disease progression and aggressiveness. [3] The expression of N-cadherin is different in different types and subtypes of RCC, which is a feature used by researchers to differentiate between them, and could be a target for therapy and diagnosis in the future. [4,5]

For those reasons, the study intended to appraise the expression of N-cadherin, its relation to clinicopathological parameters, patients` outcome, and survival, predictive and prognostic significance.

2. MATERIALS AND METHODS

Specimens and clinical data

A retrospective study of 48 consecutive cases of RCC that underwent either radical nephrectomy (36 cases) or partial nephrectomy (12 cases) along with preaortic and/or para-aortic lymphadenectomy was done in ten cases in Urosurgery Departments at the Faculty of Medicine at Alexandria University. Specimens were collected and submitted to the histopathology laboratory in the Pathology Department at the Faculty of Medicine at Alexandria University, during the period from July 2009 to November 2010. The corresponding clinical, radiological, and follow-up data of collected specimens were gathered from documents. The patients' outcomes were determined after a follow-up period determined from the date of diagnosis to the date of death or the last follow-up before termination of the study.

Histopathological examination and staging

The H&E stained full-face tissue sections were reviewed to ascertain the histological type corresponding to the Heidelberg and UICC/AJCC classification,[6] to assess the tumor grade according to the Fuhrman grading system,[7] the presence/absence of invasion and the recognition of lymph node involvement. H&E stained tissue sections of RCC were also used for the selection of two representative tumor spots building tissue microarray (TMA) block. The staging was carried out according to the 2009 TNM staging system.[8]

Tissue microarray construction

Tissue cores of 1 mm diameter were removed from the marked area on the donor block and transferred to receiver pores in the recipient paraffin block using a manual tissue arrayer punch (Beecher Instruments Inc., Sun Prairie, Wisconsin, USA) that was matched to a prearranged design. The block was heated at 40 °C for 15 minutes. H&E-stained section from the TMA blocks was used to verify the adequacy of sampling. Other sections were used for immunohistochemical staining. [9]

Immunohistochemical staining

The sections from TMA were deparaffinized in xylene, rehydrated in descending grades of alcohol. Endogenous peroxidase activity inhibited by immersion of slide in 3% hydrogen peroxide in methanol. Antigen retrieval was performed by placing the TMA slides in citrate buffer in a microwave oven. An ultra V block was applied to block nonspecific background staining. Mouse monoclonal anti-N-cadherin antibody (clone 3B9, Thermo Fisher Scientific) was applied. The sections were incubated overnight at 4 °C in a humidity chamber. The TMA slides were then washed with 10 mM phosphate-buffered saline (PBS) and incubated with rabbit anti-mouse antibody (Dako Corporation) at room temperature, and then in peroxidase-conjugated steptavidin. Finally, the colour reaction was developed using 0.5% diaminobenzidine and 0.01% hydrogen peroxide. The TMA slides were counterstained with hematoxylin stain, dehydrated in ascending grades of alcohol, cleared in xylene, and mounted. The positive control used was normal kidney tissue and colon cancer. Sections where the primary antibody had been omitted served as negative controls.

Evaluation of N-cadherin immunohistochemical staining

A light microscope Nikon 50i was used for evaluation, under ×400-power magnification. Immunohistochemical staining was assessed and scored independently by two qualified pathologists without awareness of clinicopathological characteristics or the patients' outcome. Each spot of TMA evaluated semi-quantitatively using the method described by Afrem et al. in which the immunoreactivity for N-Cadherin was graded into four categories: (0) no expression (no detectable staining), (+1) the tumor cells show <10% reactivity, (+2) the tumor cells show 10-75% reactivity, and (+3) the tumor cells show >75% reactivity. The intensity of the reaction was subjectively evaluated and scored as follows: score (1) for a weak reaction, score (2) for a moderate reaction and score (3) for a strong reaction. The final score was determined by multiplying the intensity scores with staining reactivity area scores (0,1, 2, 3, 4, 6, 9). Finally, for statistical analysis, tumors were divided into tumors with low expression (final score ≤ 4) and tumors with high expression (final score > 4).[10]

3. STATISTICAL ANALYSIS

The collected data was categorized into categorical variables and continuous variables. The statistical analysis was implemented using the IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) and the results were as follows; categorical data was displayed in number and percentage and continuous variables were revealed in the form of mean ± standard deviation. Statistical association between the different clinicopathological variables and N-cadherin expression were tested. Chi-square or the Fisher exact test was used to find the correlation between two categorical variables whereas the Mann–Whitney U test was used to assess the relationship between categorical and continuous variables. The survival analysis carried out using the Kaplan-Meier method. The level of significance was set at a $P<0.05$.

4. RESULTS

Clinicopathological data

In the current work, 48 cases of RCC were included with the mean age 50.4±15.4 years (age ranges: 18 – 95). Male to female ratio was 2:1; males were 32(66.7%) and females 16(33.3%). The mean tumor size was 9.43±5 cm (range: 2-23). In four cases (8.3%), the tumor showed multicentricity. Tumor invasion of renal sinus, renal capsule and perinephric fat, Gerota's fascia, and

Adrenal gland was as follows: Three (6.25%), 11 (23%), one (2%), and one (2%).

Lymph node metastases were established in six (60%) cases.

The histological types of RCC recognized in this study were clear cell RCC (CCRCC), papillary RCC (PRCC), chromophobe RCC (ChRCC), collecting duct RCC (CDRCC);and RCC with sarcomatoid change (SCRCC). The majority was grade 2 and 3. The tumor stages were mostly stage 1 and 4, [figure 1 and 2 show the number and percent of each]. Tumor metastasis was found in 15 (31.3%) of cases and venous invasion was in seven (14.6%) of the cases. In terms of the outcome, patients were categorized into three groups; patients with no evidence of disease (60.4%), patients who were alive with disease (31.3%), and patients who had died of their disease (8.3%). Tumor recurrence was in two (4.2%) cases only.

Immunohistochemical staining of TMA

The total number of performed spots that represented the 48 studied cases of RCC was 96, of which 90 tissue spots were informative for immunohistochemistry analysis whenever there was a missed spot or part of which the other one was informative (57 CCRCC, 21 PRCC, six ChRCC, two CDRCC, and four SCRCC spots).

Expression patterns of N-cadherin

The expression pattern of N-cadherin in tumor cells was either cytoplasmic or mixed membranous and cytoplasmic. Nuclear staining was faced, but less often. In CCRCC, cytoplasmic staining in 12 (38.7%) of cases [Figure3, 1a and b], and mixed membranous and cytoplasmic expression in 13(41.9%) of the cases, negative staining was in six (19.4%) of cases [Figure3, 2a and b]. One type I PRCC case (9.1%) showed cytoplasmic staining [Figure3, 3a and b] and two (18.2%) cases showed mixed membranous and cytoplasmic expression, whereas type II PRCC showed cytoplasmic staining in one (9.1%) case, and mixed membranous and cytoplasmic expression in 7(63.6%) of the cases [Figure3, 4a and b]. Mixed membranous and cytoplasmic expression was seen in all cases of ChRCC [Figure4, 1a and b] and CDRCC [Figure4, 2a and b]. Cytoplasmic staining was in SCRCC cases [Figure4, 3a and b].

N-cadherin showed high expression, score (1) in 41(85.4%) of RCC cases which represented in 24 (77.4%) of CCRCC and all cases of PRCC, ChRCC, CDRCC, and SCRCC, and low expression, score (0) in seven (14.6%) of CCRCC cases.

The correlations of N-cadherin immunohistochemical expression with clinicopathological factors

N-cadherin expression in tumor samples in relation to clinicopathological factors is illustrated in [figures 5-11] No significant differences were identified between expression levels of N-cadherin protein and the parameters, including age (P=0.6), gender (P=0.15), tumor size (P=0.75), histological type (P=0.34), grade (P=0.46), stage (P=0.54), metastatic status (P=0.5) and venous invasion (P=0.2).

Patients' outcome and tumor recurrence

The associations between the patients' outcome, tumor recurrence and N-cadherin expression were statistically insignificant (P=0.6), (P=0.15). The results illustrated that 25 (61%) of the cases had high expression of N-cadherin protein in patients with no evidence of disease and 40(97.6%) of the cases had high expression of N-cadherin protein in patients with no recurrence as shown in Figures 12 and 13. The survival analysis revealed a significant difference in the survival between the cases of high expression and low expression of N-cadherin (P=0.01). The better survival results were in the cases with high abnormal N-cadherin expression with a mean of estimated survival 23.2 months (95%CI: 18.4-28) as shown in Figure 14. The mean of estimated overall survival was 22 months. When cases that disappeared during follow-up (censored) were excluded, the associations between the patients' outcome and N-cadherin expression was nearly significant (P=0.05).

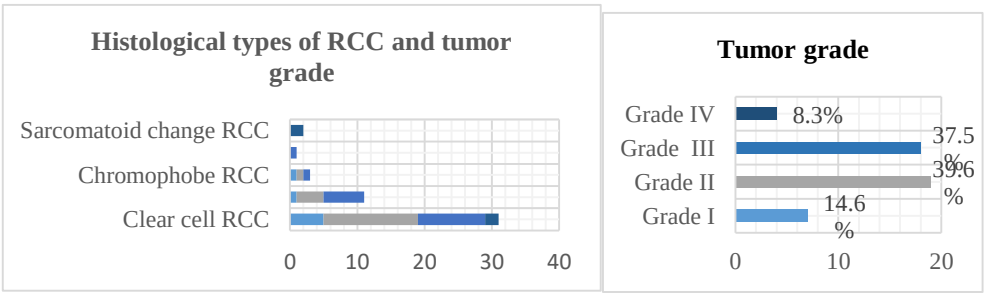


Figure 1: The histological types of RCC and tumor grade (number and percentage).

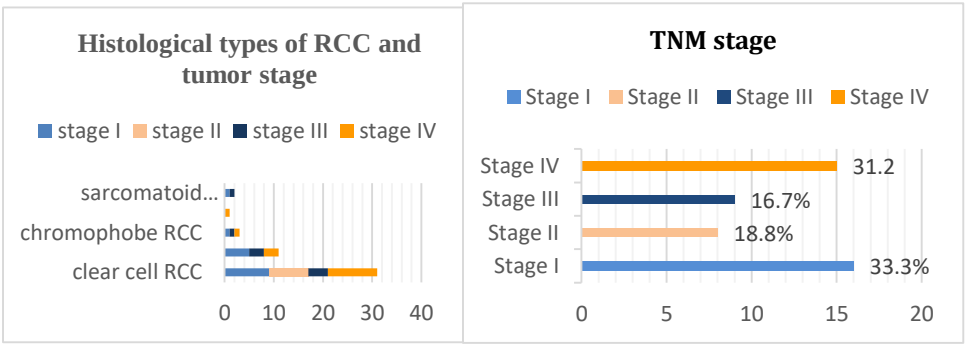


Figure 2: The histological types of RCC and tumor stage (number and percentage).

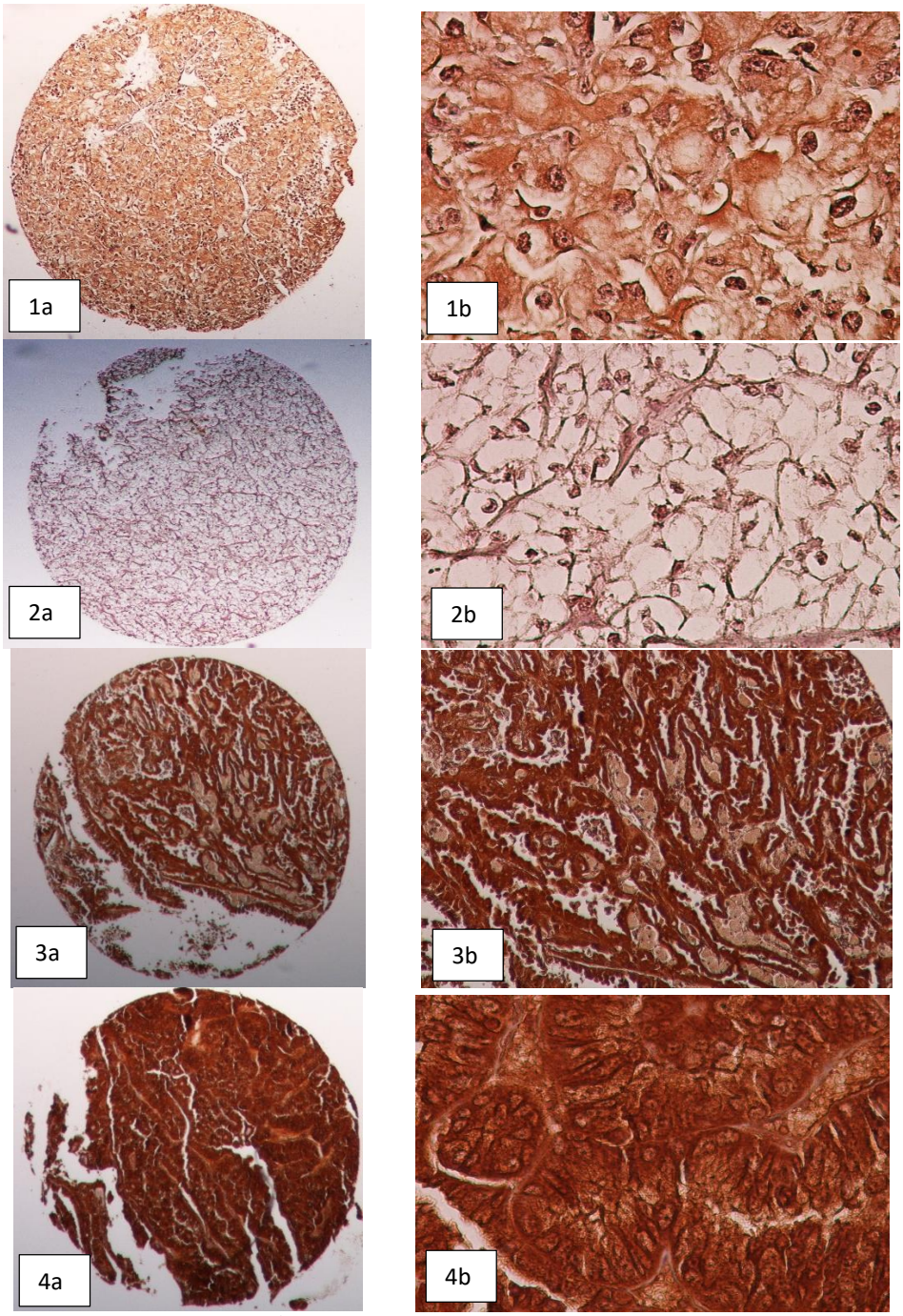


Figure 3: (1a) Tissue microarray representative spot of CCRCC shows N-cadherin cytoplasmic immunostaining (score 1) (original magnification: x40). (1b) CCRCC shows N-cadherin cytoplasmic immunostaining (score 1) (original magnification: x400). (2a) Tissue microarray representative spot of CCRCC shows N-cadherin immunostaining (score 0) (original magnification: x40). (2b) CCRCC shows N-cadherin immunostaining (score 0) (original magnification: x400). (3a) Tissue microarray representative spot of PRCC type I shows N-cadherin cytoplasmic immunostaining (score 1) (original magnification: x40). (3b) PRCC type I shows N-cadherin cytoplasmic immunostaining (score 1) (original magnification: x400). (4a) Tissue microarray representative spot of PRCC type II shows Ncadherin mixed cytoplasmic and membranous immunostaining (score 1) (original magnification: x40). (4b) PRCC type II shows N-cadherin mixed cytoplasmic and membranous immunostaining (score 1) (original magnification: x400).

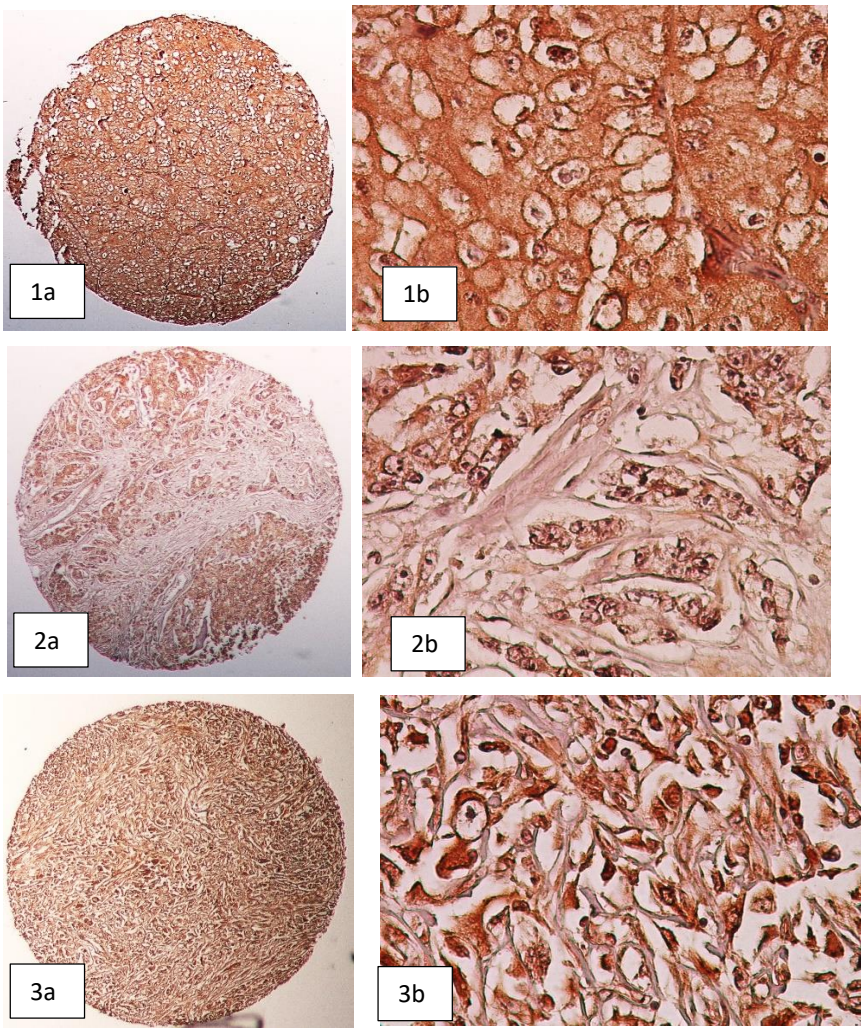


Figure 4: (1a) Tissue microarray representative spot of ChRCC shows N-cadherin mixed cytoplasmic and membranous immunostaining (score 1) (original magnification: x40). **(1b)** ChRCC shows N-cadherin mixed cytoplasmic and membranous immunostaining (score 1) (original magnification: x400). **(2a)** Tissue microarray representative spot of CDRCC shows N-cadherin mixed cytoplasmic and membranous immunostaining (score 1) (original magnification: x40). **(2b)** CDRCC shows N-cadherin mixed cytoplasmic and membranous immunostaining (score 1) (original magnification: x400). **(3a)** Tissue microarray representative spot of SCRCC shows N-cadherin cytoplasmic immunostaining (score 1) (original magnification: x40). **(3b)** SCRCC shows N-cadherin cytoplasmic immunostaining (score 1) (original magnification: x400).

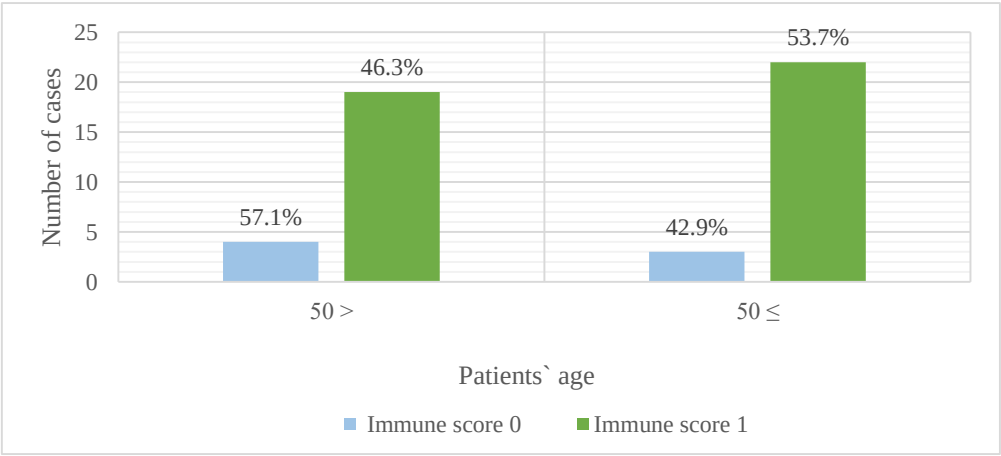


Figure 5: The relationship between N-cadherin expression in RCC and patients' age.

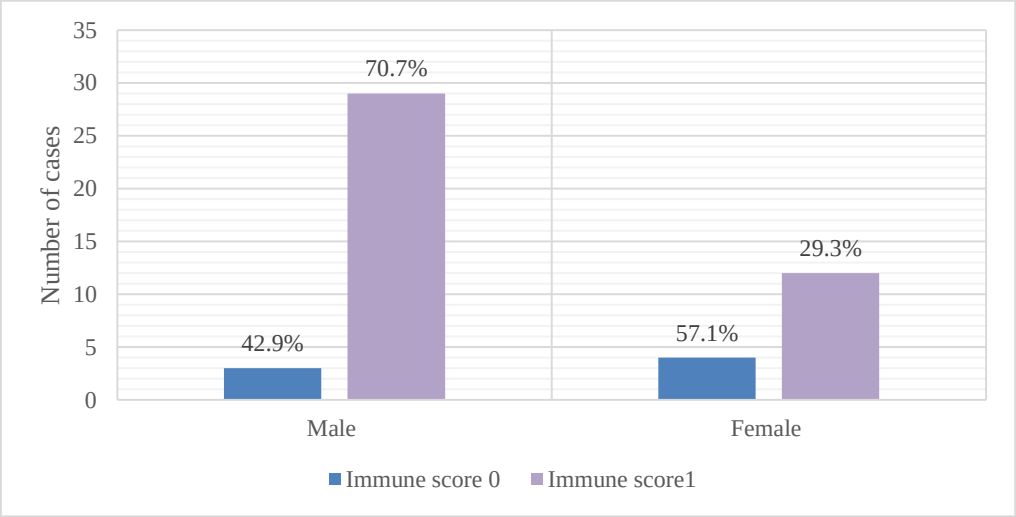


Figure 6: The relationship between N-cadherin expression in RCC and patients' gender.

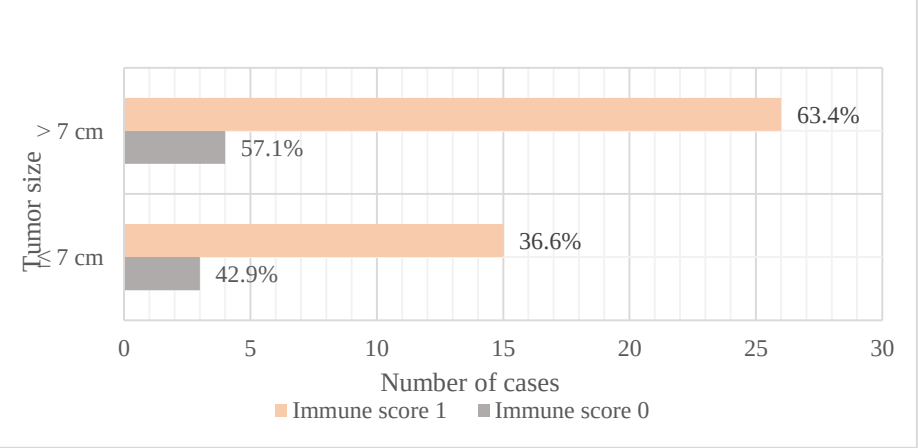


Figure7: The relationship between N-cadherin expression in RCC and tumor size.

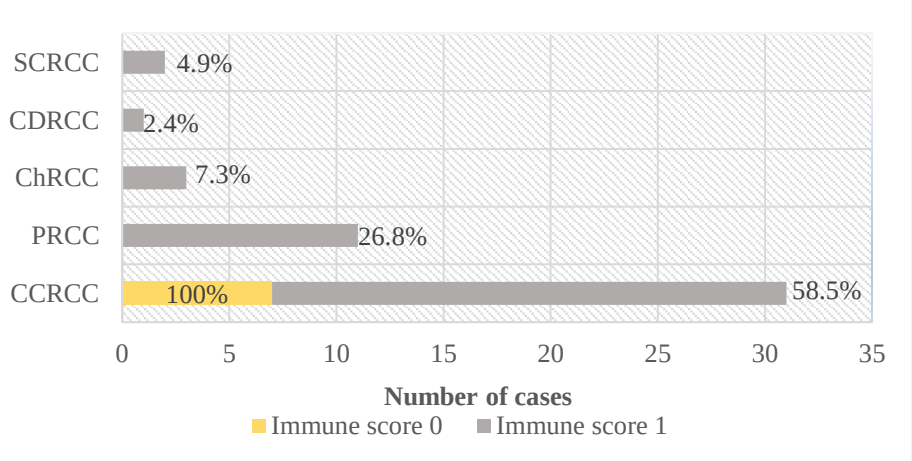


Figure 8: The relationship between N-cadherin expression in RCC and histological types of RCC.

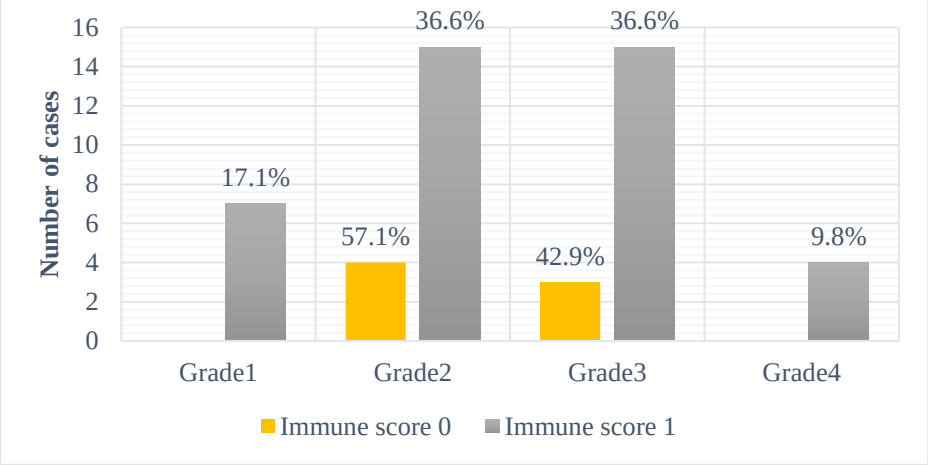


Figure 9: The relationship between N-cadherin expression in RCC and tumor grade.

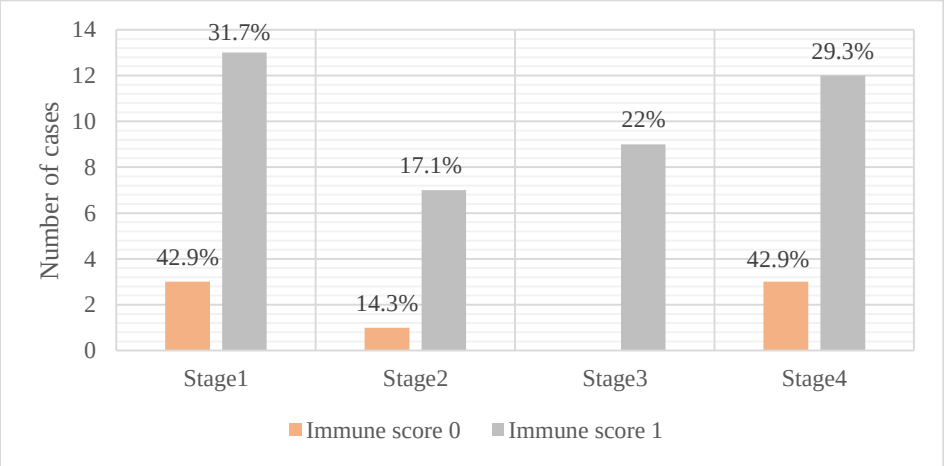


Figure 10: The relationship between N-cadherin expression in RCC and tumor stage.

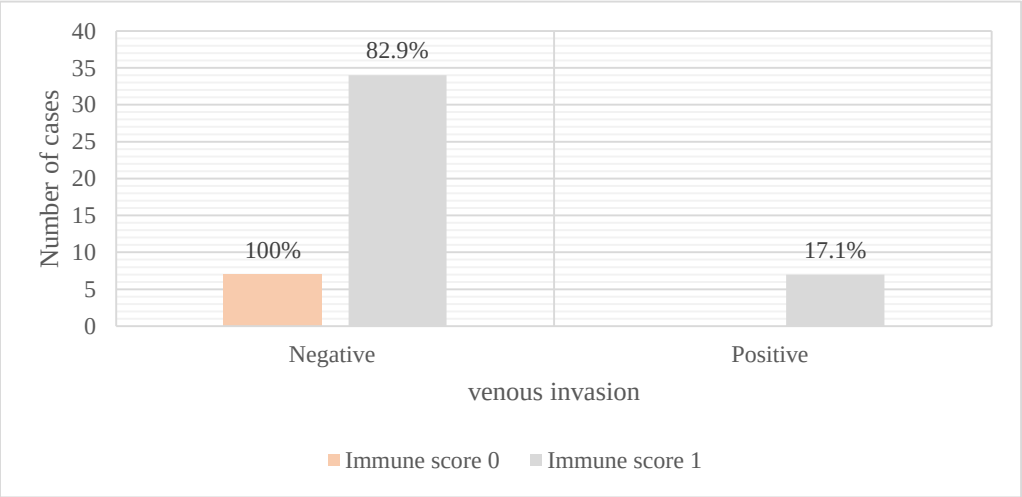


Figure 11: The relationship between N-cadherin expression in RCC and venous invasion.

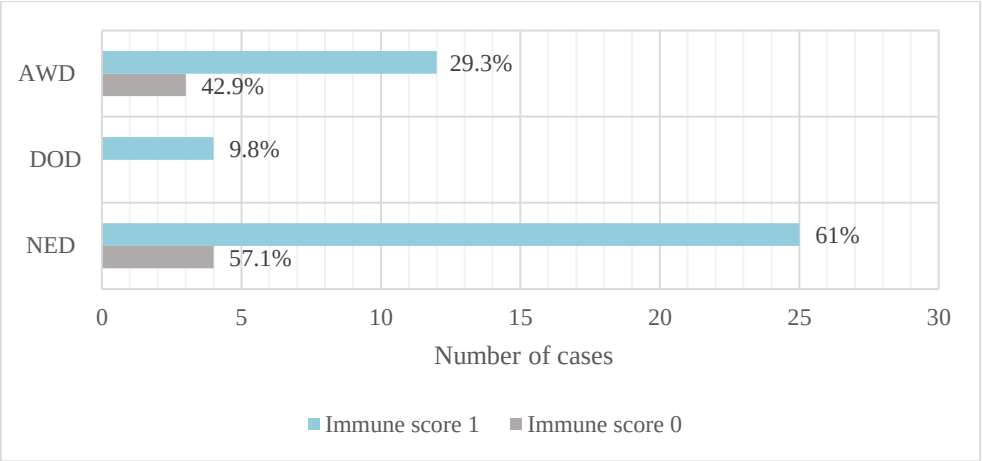


Figure 12: The relationship between N-cadherin expression in RCC and patients' outcomes.

(AWD, alive with disease; DOD, died of disease; NED, no evidence of disease)

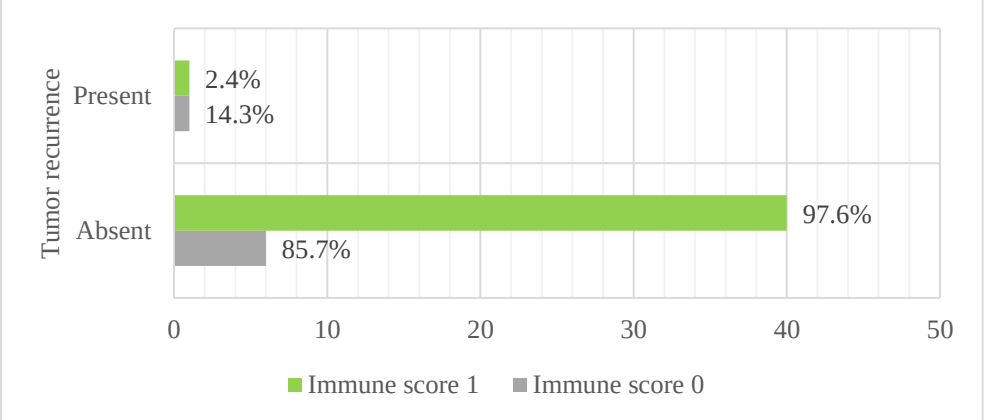


Figure 13: The relationship between N-cadherin expression in RCC and tumor recurrence.

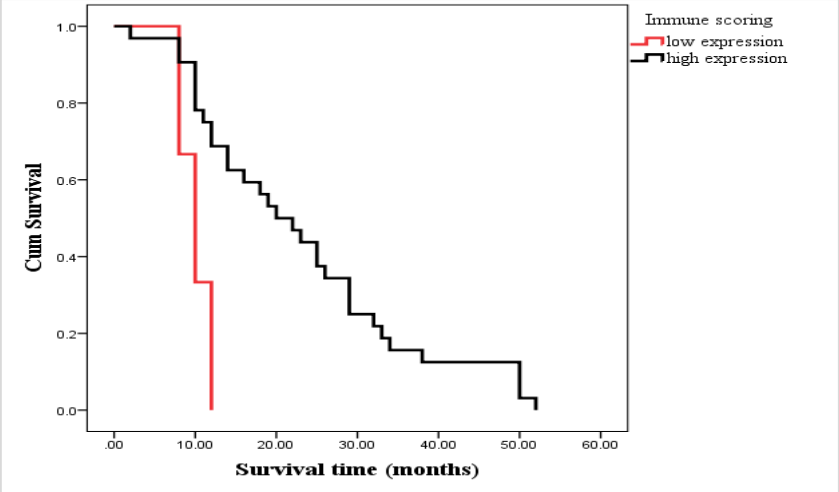


Figure 14: Plot of the Kaplan-Meier survival estimate revealed better survival in the cases that showed abnormal high expression of N-cadherin (*P*=0.01).

5. DISCUSSION

N-cadherin overexpression has been observed in many epithelial tumors such as lung cancer, prostate cancer, pancreatic cancer and oral squamous cell carcinoma, associated generally with tumor aggressiveness and poorer patient prognosis.[3]

In the present study, immunohistochemical analysis of N-cadherin was carried out in 48 cases comprising different histological types of RCC. In tumor cells, immunoreactivity was either cytoplasmic or mixed membranous and cytoplasmic staining. The expression of this protein determines its role as a cell adhesion molecule when other cadherins are impaired.[11]

In the present work, mixed membranous and cytoplasmic expression was seen in 7(63.6%) of type II PRCC cases and two (18.2%) of type I PRCC cases, whereas cytoplasmic staining was seen in one (9.1%) of type I PRCC and one (9.1%) case of type II PRCC cases. These results were different from the findings described by Behnes et al. that disclosed N-cadherin membranous positivity in all cases of type II PRCC whereas cytoplasmic expression of N-cadherin was in type I PRCC.[12] The difference in the sample size, immunostaining method, and tumor characteristics adhesion molecules made variations in the results.[2,12,13]

Mixed membranous and cytoplasmic expression was seen in all cases of ChRCC in this work, in contrast to a study done by Badowska-Kozakiewicz et al. which showed that all cases of ChRCC were lacking N-cadherin expression.[5]

Mixed membranous and cytoplasmic expression was seen in the case of CDRCC in the current work. A study accomplished by Tani T et al. proposed that most RCCs co-express the adhesion molecules distinctive of both proximal and distal tubules (E- and N-cadherins).[13]

In this study, cytoplasmic staining was seen in SCRCC cases. The same finding was in a study conducted by Shimazui T et al.[11] and a study done by Conant JL et al. proposed that the expression of N-cadherin involved early in initiating EMT as a mechanism for the development of sarcomatoid change in RCC.[14]

The relationship between N-cadherin and the clinicopathological characteristics of the patients has been addressed in this study; the association between N-cadherin expression and tumor size was statistically insignificant, though high N-cadherin expression was seen in 26 (63.4%) of cases with large tumor size. A study accomplished by Jang NR et al. showed a significant association between the high N-cadherin expression and larger tumor size.[15]

Regarding histological types of RCC, no statistical correlation with N-cadherin expression was observed in this study. A similar finding in a study conducted by Shimazui T et al.[11] was explained by the difference in of the number of RCC types in the sample under study.

There was no established association between N-cadherin immunoexpression and pathological parameters, i.e. stage and grade. The same observation was demonstrated by Shimazui T et al. [11] and Gasinska A et al.[2] In contrast to this study, in other malignancies like esophageal cancer and brain gliomas, a correlation of N-cadherin expression with tissue invasion was observed. N-cadherin expression may be associated with depth of invasion in the case of esophageal cancer [16], and expression of N-cadherin correlated with a decreased invasion in the case of high-grade gliomas [17], indicating the functional role of N-cadherin in tissue integrity.

In the present work, the relation between N-cadherin and metastatic status of the patients, and venous invasion were statistically insignificant, and the noted 29 (70.7%) of cases with high expression pattern had no metastasis, also 34(82.9%) of cases with high expression pattern had no venous invasion. A study by Gasinska A et al. clarifies this finding, and shows that ‘’the change from epithelial to mesenchymal phenotype based on higher expression of vimentin, N-cadherin, Ki-67, survivin and also repression of E-cadherin and PTEN which may demonstrate an increased potential for metastasis’’.[2] So to assess the metastatic potential, assessment of other proteins along with N-cadherin is needed.

In this work, although there was no significant association between the patients’ outcome and N-cadherin expression,there was a significantly better survival result in cases with high abnormal N-cadherin expression. Similarly, survival curve in a study performed by Shimazui T et al.[11] showed that normal N-cadherin expression in RCC patients was associated with an inferior prognosis in comparison to those whose tumor expressed an abnormal pattern. In contrast, a study done by Jang NR et al. showed the abnormal expression of E-cadherin, N-cadherin, and P-cadherin was associated with adverse clinicopathological factors, worse overall survival, and poor outcomes.[15]

The association between the tumor recurrence and N-cadherin expression in the cases under study were statistically insignificant and showed 40 (97.6%) of the cases had high expression of N-cadherin protein in patients with no recurrence. However, comparing this finding with a study conducted by Muramaki M et al. disclosed conclusions that suggest that reduced E-cadherin and increased expression of N-cadherin in RCC is associated with disease recurrence following radical nephrectomy.[18]

6. CONCLUSION

There is a significant association between N-cadherin expression pattern and the survival of patients with RCC disclosed better survival in cases with high abnormal N-cadherin expression and therefore the better prognosis. There were no associations between N-cadherin expression and patients' age and gender, tumor characteristics, patients' outcome and tumor recurrence. The results were discussed according to the findings in the previous studies. The value of the use of N-cadherin alone as marker in predicting the course and outcome, and to select patients for specific treatment is not sufficient. More in vivo and in vitro studies are needed for further elucidation of the role of N-cadherin and how it is involved in RCC.

7. LIMITATION OF THE STUDY

The low number of patients as total in the sample and the low number of patients in histological types under study may have affected the results we obtained.

8. CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this paper.

9. REFERENCES

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