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Correlation between N-Cadherin and MMP-7 expression in regional clear cell renal cell carcinoma regional node metastasis status

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Abstract

Clear Cell Renal Cell Carcinoma (ccRCC) is the most common subtype of renal malignancy and is frequently diagnosed at an advanced stage due to non-specific early symptoms. Regional lymph node metastasis represents an important prognostic factor in ccRCC and is closely related to tumor invasiveness. Biological processes such as Epithelial Mesenchymal Transition (EMT), involving N-Cadherin, and extracellular matrix degradation mediated by matrix metalloproteinase-7 (MMP-7), are believed to contribute to metastatic progression. However, the relationship between these biomarkers and regional lymph node status in ccRCC remains insufficiently clarified, particularly in the Indonesian population. This study aimed to analyze the differences and correlations between N-Cadherin and MMP-7 expression and regional lymph node metastasis status in ccRCC. An analytical observational study with a cross-sectional design was conducted using 45 paraffin-embedded ccRCC nephrectomy specimens. Immunohistochemical staining for N-Cadherin and MMP-7 was evaluated using the H-score method. Statistical analysis included the Kruskal Wallis test and Spearman's correlation. The results demonstrated a significant difference and positive correlation between MMP-7 expression and lymph node metastasis status, whereas N-Cadherin showed an increasing trend without statistical significance. A significant positive correlation was observed between N-Cadherin and MMP-7 expression. In conclusion, MMP-7 appears to be a stronger indicator of regional lymph node metastasis in ccRCC than N-Cadherin. The combined expression of N-Cadherin and MMP-7 may serve as a potential biomarker panel for prognostic assessment and risk stratification in ccRCC.

Keywords: Clear cell renal cell carcinoma, N-Cadherin, MMP-7, Lymph node metastasis, Immunohisto chemistry.

Introduction

Clear Cell Renal Cell Carcinoma (ccRCC) is the most common histological subtype of renal cancer, accounting for approximately 70–85% of cases according to the WHO. However, it is often diagnosed at an advanced stage due to non-specific early symptoms and the absence of effective screening tools, which consequently leads to a poor prognosis (Naghdibadi et al., 2023; Yang et al., 2023; Arora & Limaiem, 2023). Resistance to surgery, radiotherapy, and chemotherapy in advanced stages is frequently influenced by tumor heterogeneity and alterations in cellular signaling pathways (Schiavoni et al., 2023; Bui et al., 2023; Raghubar et al., 2022).

Clinically, the N status (regional lymph node metastasis) in the TNM classification system serves as a critical determinant of both therapy and prognosis, as lymph node involvement correlates with lower overall survival (Yang et al., 2023; Abbas et al., 2025). Biologically, the epithelial–mesenchymal transition (EMT) process promotes invasion and metastasis through the loss of epithelial characteristics and the acquisition of a mesenchymal phenotype. The so-called "cadherin switch," characterized by increased N-Cadherin expression, enhances the migratory and invasive capacity of tumor cells (C. C. Wang et al., 2019; Gonzalez-Avila et al., 2019; Y. Wang et al., 2013; Wu & Zhou, 2010). Concurrently, matrix metalloproteinase-7 (MMP-7) degrades the Extracellular Matrix (ECM), thereby facilitating invasion. Overexpression of both N-Cadherin and MMP-7 has been associated with poorer prognosis in ccRCC, positioning them as potential prognostic biomarkers (Zannettino et al., 2018; H. Lu et al., 2013; Gonzalez-Avila et al., 2019).

Nevertheless, the precise mechanisms linking EMT particularly N-Cadherin and the proteolytic activity of MMP-7 to regional lymph node metastasis in ccRCC remain incompletely elucidated. To date, no clinically approved therapies specifically targeting the N-Cadherin pathway have been established (Schiavoni et al., 2023). This evidentiary gap holds clinical relevance, especially in Indonesia, where local data remain scarce.

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Therefore, this study aims to analyze the differences and correlations in N-Cadherin and MMP-7 expression across various regional lymph node metastasis statuses in ccRCC, including the relationship between each marker and lymph node involvement as well as their combined correlation. The goal is to clarify their prognostic value and identify potential opportunities for risk stratification and the development of more precise therapeutic targets (Naghdibadi et al., 2023; Yang et al., 2023).

Methods

1. Study design

This was an analytical observational study with a cross-sectional design assessing the association between N-Cadherin and MMP-7 expression and regional Lymph Node (LNs) metastasis status in patients with Clear Cell Renal Cell Carcinoma (ccRCC). The study was conducted after obtaining ethical approval from the Health Research Ethics Committee of RSUD Dr. Soetomo, Surabaya. Study sites were the Anatomic Pathology Unit, Central Laboratory RSUD Dr. Soetomo, and the Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya. The study period was six months from protocol approval.

2. Population and samples

The target population comprised all ccRCC tumor tissues archived as paraffin blocks from January 2014 to December 2023, with histopathologic diagnoses established according to the WHO Classification of Urinary and Male Genital Tumours, 5th edition (2022). The study sample consisted of ccRCC nephrectomy paraffin blocks confirmed by certified anatomic pathologists and categorized into N0 (no regional LN metastasis) and N1 (with regional LN metastasis) based on radiologic (CT scan) and histopathologic findings.

Inclusion criteria were well-preserved paraffin blocks containing adequate tumor cells. Exclusion criteria were ccRCC nephrectomy with Nx cases, concomitant malignancies and second-opinion cases. Sampling employed a purposive approach. The minimum required sample size was 43; applying a 15% correction to mitigate potential error yielded a final target of 50 samples.

3. Equipment and reagents

Equipment included a Leica microtome, Olympus CX31 binocular light microscope, Olympus DP2-BSW documentation system, staining jars, a Leica paraffin bath, pipettes, glass slides/coverslips, and forceps. Reagents comprised paraffin blocks; monoclonal antibodies to N-Cadherin and MMP-7; secondary antibody (Trekkie Link) and HRP-labeled secondary; TRS/citrate buffer; background snipper; xylene; PBS; DAB; Mayer's hematoxylin; and graded alcohols (80–96%); plus, glycerol.

4. Procedures

Case identification used medical record numbers and histopathology accession numbers from the Anatomic Pathology archives. Hematoxylin–eosin (HE) slides were re-reviewed blinded by two anatomic pathologists and the investigators to confirm diagnoses and re-assess LN status per operational definitions. Eligible paraffin blocks were sectioned at 3–5 µm, mounted on slides, deparaffinized in xylene, and rehydrated through graded alcohols (96%, 90%, 80%).

Endogenous peroxidase was blocked with 3% H_2O_2 in methanol for 15 minutes at room temperature, followed by antigen retrieval using Target Retrieval Solution / citrate buffer (pH 6) at 95 °C for 20 minutes. After PBS rinses, background snipper was applied for 15 minutes. Primary monoclonal antibodies against N-Cadherin and MMP-7 were applied (room temperature, 60 minutes), followed by a secondary antibody (Trekkie Link, 20 minutes) and an HRP-labeled secondary (10 minutes). Signal was visualized with diaminobenzidine (DAB) and counterstained with Mayer's hematoxylin. Slides were then dehydrated through graded alcohols, cleared in xylene, and coverslipped.

5. Data analysis

Immunohistochemical results were evaluated using the Olympus CX31 by two independent raters per operational criteria and recorded on standardized data sheets. Descriptive statistics summarized clinicopathologic characteristics (sex, age, LN status).

One-sample Kolmogorov–Smirnov tests assessed normality and homogeneity. Differences in N-Cadherin and MMP-7 expression across LN status were analyzed using ANOVA when assumptions were met, or Kruskal–Wallis when violated. Correlations between N-Cadherin and MMP-7 expression were tested using Pearson's correlation for normal/homogeneous data or Spearman's rank correlation for non-normal/heterogeneous data. A two-sided $p < 0.05$ indicated statistical significance.

Table 1. Characteristics of study samples

Variable	N0	N1	Total n (%)
Age Group (years)			
16-25	2	0	2 (4,44)
26-35	1	1	2 (4,44)
36-45	4	3	7 (15,56)
46-55	8	9	17 (37,78)
56-65	7	5	12 (26,67)
66-75	3	2	5 (11,11)
Sex			
Male	11	13	24 (53,33)
Female	14	7	21 (46,67)
Total (n)	25	20	45

Results

This study evaluated differences and correlations in N-Cadherin and MMP-7 expression across regional lymph node (LN; N stage) status in clear cell renal cell carcinoma (ccRCC). A total of 45 cases were analyzed: N0 25 (55.56%) and N1 20 (44.44%). The age range was 16-75 years (mean 51.49; median 51), peaking at 46–55 years (37.78%), followed by 56–65 years (26.67%). Males predominated (53.33%); N0 was more frequent in females, whereas N1 predominated in males (Table 1).

Immunohistochemical expression was scored using the H-score (0–300), combining staining intensity and the percentage of positive tumor cells, categorized as negative (0–49), weak (50–99), moderate (100–199), and strong (200–300). Assessments were performed double-blind by two pathologists with an allowed inter-rater difference ≤30. The Kruskal–Wallis test showed that N-Cadherin tended to increase with advancing N stage (mean rank N0 = 19.76; N1 = 27.05), but the difference was not significant (Chi-square 3.433; df = 1; p = 0.064). In contrast, MMP-7 differed significantly across N stages (mean rank N0 = 19.36; N1 = 27.55; Chi-square 4.338; df = 1; p = 0.037). Descriptively, the mean MMP-7 expression increased from 19.36 (N0) to 27,55 (N1), consistent with a dose–response pattern relative to LN involvement (Table 2).

Table 2. Kruskal–Wallis test and ranking analysis of marker expression by lymph node metastasis

Variable	Stage	n	Mean Rank	Chi-Square	df	Sig (p-value)	Interpretation
N-Cadherin	N0	25	19.76	3.433	1	0.064	No significant difference (p = 0.064)
	N1	20	27.05				
MMP-7	N0	25	19.36	4.338	1	0.037	Significant difference among N stages (p < 0.05)
	N1	20	27.55				

Associations were examined using Spearman's non-parametric correlation (non-normal data; Table 3). The findings indicate that higher MMP-7 expression is associated with more advanced N stage, whereas N-Cadherin alone showed no significant association, despite a direction of effect consistent with increasing tumor aggressiveness.

Table 3. Correlation between N-Cadherin, MMP-7 expression, and regional lymph node metastasis status in Clear Cell Renal Cell Carcinoma (ccRCC)

Variable	R (Correlation)	P-value	Interpretation
N-Cadherin expression vs. N stage	0.279	0.063	No significant correlation
MMP-7 expression vs. N stage	0.314	0.036	Significant correlation
N-Cadherin vs. MMP-7	0.376	0.011	Significant correlation

Overall, these results position MMP-7 as a stronger indicator of regional LN metastasis status in ccRCC than N-Cadherin. The positive relationship observed with co-expression supports the potential use of a biomarker panel for risk stratification. Clinically, MMP-7 merits consideration as a candidate prognostic biomarker and for further testing in strategies to estimate nodal metastasis risk, whereas N-Cadherin requires validation with larger sample sizes and standardized scoring to clarify its role in the ccRCC context.

Discussions

The subject characteristics indicate that Clearest Cell Renal Cell Carcinoma (ccRCC) cases occurred in middle-aged to older adults (mean 51.49 years; median 51 years), with peaks at 46–55 years (37.78%) and 56–65 years (26.67%), consistent with global epidemiology showing that ccRCC is commonly diagnosed in the 5th–7th decades (Capitanio & Montorsi, 2016). The presence of a 17-year-old case aligns with reports of early-onset disease linked to genetic predisposition, such as von Hippel–Lindau syndrome (Linehan et al., 2019). The relatively high N1 proportion (42.55%) compared with international cohorts (≈20–30%) may reflect intratumoral heterogeneity, diagnostic delays, and limited sample size in advanced stages (Golijanin et al., 2019; Capitanio et al., 2019; Gerlinger et al., 2012; Turajlic et al., 2018). Males predominated (55.32%), mirroring the global ~2:1 ratio (Capitanio & Montorsi, 2016). Notably, N0 was more frequent in females and N1 in males, consistent with biological hypotheses (estrogen's protective effects on angiogenesis/invasion and potentially higher expression of invasive biomarkers—e.g., N-Cadherin, MMPs—in men) (Ljungberg et al., 2019; Linehan et al., 2019). These variations are likely reinforced by heterogeneity in EMT/adhesion pathways in ccRCC (Gerlinger et al., 2012; Turajlic et al., 2018).

Biologically, N-Cadherin plays a central role in EMT through the cadherin switch, enhancing motility and invasion via downstream signaling (FGFR/ERK, PI3K/AKT) that promotes cytoskeletal reorganization and apoptosis resistance; collectively, this facilitates lymphatic dissemination (Loh et al., 2019; Yusuf et al., 2023; Ghantous et al., 2024). Multiple studies associate high N-Cadherin expression with increased lymph node involvement and worse outcomes (Wang et al., 2016; Mrozik et al., 2018; Luo et al., 2018; Zhang et al., 2024), including cross-epithelial tumor evidence (e.g., gastric, nasopharyngeal cancers) linking strong expression with more advanced N stage (Okubo et al., 2017; Yusuf et al., 2023). However, our study did not find a correlation between N-Cadherin and nodal status. This discrepancy may be explained by ccRCC's unique biology—dominant angiogenesis driven by VHL inactivation/HIF–VEGF activation and a propensity for hematogenous spread—attenuating the contribution of N-Cadherin to lymphogenous metastasis; intratumoral variation and IHC scoring approaches may further influence results (Linehan et al., 2013; Joshi et al., 2015; Chouiri et al., 2017; Turajlic et al., 2018; Ricketts et al., 2018; Liu et al., 2023).

In contrast, MMP-7 shows a more consistent relationship with nodal metastasis. As a matrix protease, MMP-7 degrades ECM (proteoglycans, laminin, fibronectin) and cleaves E-cadherin, accelerating EMT, motility, and invasive phenotypes; it also activates pro-TNFα/pro-HB-EGF and reinforces Wnt/β-catenin and PI3K/AKT signaling—highly relevant in hypoxic ccRCC (Zakiyanov et al., 2019; Liao et al., 2021; Wei et al., 2024). Clinically, elevated MMP-7 correlates with lymphovascular invasion, nodal involvement, and poor prognosis in RCC and gastrointestinal malignancies (Urushibara et al., 2018; Wattanawongdon et al., 2022; Wei et al., 2024). Our findings are concordant: mean MMP-7 expression was higher in N0 than N1 (55.56 → 44.44), reflecting a biological dose–response and supporting MMP-7 as an independent predictor of nodal metastasis and a potential therapeutic target (Kovács et al., 2022; Yuan et al., 2020; Kubik et al., 2023).

The N-Cadherin–MMP-7 interaction has a mechanistic basis: MMP-7 can cleave cadherin ectodomains (including N-Cadherin), weakening adhesion and modulating pro-survival/pro-inflammatory signaling, while their co-expression associates with more aggressive invasion/metastasis (Williams et al., 2010; Conant et al., 2017; Zhang et al., 2016; Luan et al., 2023; Mrozik et al., 2018; Mustafa et al., 2022). In this study, although N-Cadherin alone did not correlate with nodal status, its co-expression pattern with MMP-7 tracked with metastatic

progression, underscoring their value as a panel for risk stratification and opening the door to dual-targeted therapeutic strategies in ccRCC.

Conclusion

In this cross-sectional series of 45 ccRCC cases, the cohort was dominated by middle-aged to older males, with a relatively high N1 proportion. H–score–based IHC showed MMP-7 expression increased with higher N stage and differed significantly across groups (Kruskal–Wallis p = 0.037), correlating positively with nodal involvement (rho = 0.314; p = 0.036). N-Cadherin exhibited only a non-significant upward trend (p = 0.064) and did not correlate with nodal status (rho = 0.279; p = 0.063). Nevertheless, co-expression of N-Cadherin and MMP-7 correlated positively with nodal status (rho = 0.376; p = 0.011), suggesting a useful biomarker panel for risk stratification. Overall, MMP-7 emerges as a stronger and potentially prognostic indicator of nodal metastasis in ccRCC than N-Cadherin, supporting further exploration of MMP-7 as a therapeutic target. Limitations—sample size, and cross-sectional design—warrant multi-center, larger, and longitudinal studies to validate these biomarkers' roles in clinical decision-making.

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