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Claudin as a prognostic factor in renal cell carcinoma: Systematic review

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Abstract

To analyse claudin expression as a molecular prognostic factor in renal cell carcinoma. Several databases were used to compile data for a cohort research on claudin expression in patients with renal cell carcinoma who had undergone nephrectomy. These databases included cancer-specific survival, disease-free survival, overall survival, and cumulative survival rate. This review included ten studies involving 2,192 adult patients diagnosed with renal cell carcinoma (RCC) who underwent nephrectomy, to analyse the correlation between claudin expression and clinicopathological features. This review included 696 female patients and 1,371 male patients. All participants were adults, with a median and mean age exceeding 60 years. Claudin expression varied across studies and correlated with specific clinicopathological characteristics. Dysregulation of claudin-4 and claudin-8 was associated with more aggressive histopathological features, characterised by higher tumour grade and advanced stage, while claudin-5 and claudin-6 demonstrated no significant association with clinicopathological features. In renal cell carcinoma, overexpression of claudin-1 and claudin-10 was substantially linked to worse Cancer-Specific Survival (CSS), although elevation of claudin-7 had no such association. The opposite was true for Disease-Free Survival (DFS), which improved with increased levels of claudin-7 and claudin-10. Additionally, in renal cell carcinoma, there was no statistically significant association between claudin-6 expression and Overall Survival (OS), although overexpression of claudin-7, claudin-8, and claudin-10 was related with greater OS. According to this systematic review, claudin family proteins may serve as potential molecular prognostic markers and therapeutic targets in renal cell carcinoma. Confirmation to these indications through large-scale, prospective studies integrating molecular, genomic, validation of these associations and clarification of the function of claudins in kidney tumor growth and therapy response need more clinical data.

Keywords: Cancer, Kidney cancer, Renal cell carcinoma, Claudin, Cancer-Specific survival, Disease-Free survival, Overall survival, Cumulative survival.

Introduction

Among all cancers, renal cell carcinoma ranks fourteenth. There were approximately 431,288 new cases in 2020, representing 2.2% of all cancer incidences and 1.8% of total cancer-related deaths (Qi et al., 2021; Schiavoni et al., 2023). In 2020, GLOBOCAN revealed that 271,000 cases of renal cell carcinoma were diagnosed in men and 160,000 in women (Schiavoni et al., 2023). There are several subtypes of renal cell carcinoma (RCC) based on histology and genetics. About 60%-75% of all instances of renal cell carcinoma in adults are ccRCC, the most prevalent sporadic subtype of the disease (Amin et al., 2022; Schiavoni et al., 2023).

Tumour size is a cornerstone of the TNM staging system and a key prognostic factor in renal cell carcinoma. After nephrectomy, the 5-year cancer-specific survival (CSS) rate for renal cell carcinoma (RCC) localized to the kidney (pathological stage pT1-2) ranges from 71% to 97%, which is the best prognosis. The 5-year recurrence-free survival (RFS) rates were 75.6% and 86.9%, respectively, while the 10-year RFS rates were 80.8% and 59.5%, according to a research by Klatte et al. that included 519 patients with renal carcinoma, some of whom had capsular invasion and others who did not. Another study of patients with localised RCC (without capsular invasion) demonstrated a 10-year CSS rate of 90.6%, compared to 69.5% among those with capsular invasion. Similarly, May et al. reported that patients with RCC without capsular invasion had 5-year RFS and CSS rates of 92.3% and 95.7%, respectively, while those with capsular invasion had lower rates of 77.7% and 85.5%, the capsular invasion is an independent prognostic factor, and there is a significant difference in CSS among patients with pT2-stage illness, according to a research by Jeong et al., which included 288 patients with clear cell renal cell carcinoma (ccRCC) who had radical nephrectomy. The recurrence risk and cancer-related mortality increased by 3.36- and 4.03-fold, respectively (Cho et al., 2009; Song et al., 2013).

Capsular invasion is facilitated by a complex

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interaction of molecular mechanisms, including activity of Matrix Metalloproteinases (MMPs), Epithelial-To-Mesenchymal Transition (EMT), disruption of cell–cell adhesion, and alterations in the Extracellular Matrix (ECM), all of which enable tumour cells to migrate and invade the renal capsule (Taneja & Williamson, 2018). In both endothelial and epithelial cell sheets, tight junctions help cells stick together and are essential for keeping cells polarity, adhesion, and permeability in check. The structural membrane proteins (such as occludin and claudins) and the Junctional Adhesion Molecules (JAMs) are the two main types of proteins found in tight junctions. Among these proteins, claudins are the most essential components, as no paracellular barrier can form in their absence (Dang et al., 2023).

Dysregulation of specific claudin isoforms has been identified in various carcinomas. Either upregulation or downregulation of claudin expression has been identified to modulate cellular proliferation, growth, metabolism, metastasis, and stem cell properties. The epithelial-to-mesenchymal transition (EMT) represents one of the most critical functional pathways through which claudin proteins contribute to cancer progression (Li, 2021; Wang et al., 2022). Furthermore, reduced claudin expression directly affects the integrity of tight junctions in conjunction with other integral membrane proteins, including zonula occludens-1 (ZO-1), leading to increased membrane permeability and facilitating tumour cell invasion through the renal capsule (Van Itallie et al., 2006).

Tumor size as a single prognostic factor may be insufficient to fully represent the biological heterogeneity of tumour cells, even in cases of Renal Cell Carcinoma (RCC) confined to the kidney. Renal capsular invasion is introduced as an additional prognostic marker for RCC. Renal capsular invasion is defined as the presence of tumour cells within the capsule, infiltrative tumour growth extending into the capsule, or direct tumour penetration through the capsule (Cho et al., 2009; Song et al., 2013; Taneja & Williamson, 2018). This capsular invasion is considered an adverse prognostic factor, as it indicates an increased potential for tumour dissemination and recurrence (Cho et al., 2009; Taneja & Williamson, 2018). Integrating capsular invasion into prognostic evaluation models for patients with pT1–2 cancers markedly improves the predictive accuracy of the TNM staging system concerning overall survival (Cho et al., 2009; Song et al., 2013).

This systematic review evaluates the association between claudin expression and Renal Cell Carcinoma (RCC) based on patient survival outcomes, primarily utilizing immunohistochemical analysis.

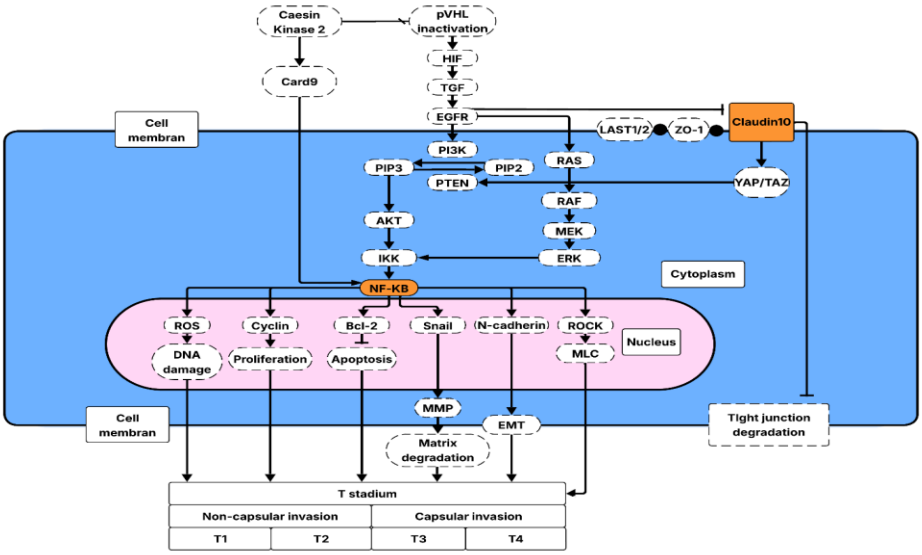

Figure 1. Claudin regulation related to capsular invasion in renal cell carcinoma

Material and Methods

In order to ensure that this systematic review followed the recommended procedures for reporting meta-analyses and systematic reviews, the writers used the PRISMA standards (Figure 1). With the registration number CRD420251157273, this review's protocol was entered into the International Prospective Register of Systematic Reviews (PROSPERO). This review utilized the PICO framework (participants, interventions, comparisons, and outcomes), included patients with histologically confirmed renal cell carcinoma, evaluated claudin expression, and survival outcomes, including cancer-specific survival, disease-free survival, overall survival, and cumulative survival.

Searching strategy

Relevant studies from recent decades investigating *claudin* expression in renal cell carcinoma were identified through systematic searches in Google Scholar, PubMed, and ScienceDirect using the keywords "renal cell carcinoma", "claudin", and "prognosis", in combination with related MeSH terms, synonyms, and expanded search expressions. The authors limited literature search to publications in Indonesian and English, covering the period between 2008 and 2024. The authors independently review the titles, abstracts, and full text from the retrieved articles. The authors resolved any discrepancies through discussion. Rayyan software was used to identify and remove duplicate literature.

Selection criteria

Inclusion criteria (guidelines for selecting the eligible studies to be included in the analysis) and exclusion criteria were established as follows: the inclusion criteria in this study were : (1) Studies involving patients with histopathologically confirmed renal cell carcinoma who underwent either radical or partial nephrectomy; (2) Studies of non-Randomized Controlled Trial (non-RCT) or cohort designs; (3) Studies published in Indonesian or English; (4) Studies published as full-text; (5) Studies specifically analysing claudin expression and its association with clinicopathological parameters or survival outcomes (e.g., cancer-specific survival, disease-free survival, overall survival, or cummulative survival). The exclusion criteria in this study were: (1) Studies that were not accessible in full text; (2) Case reports, case-control studies, reviews, and conference abstracts; (3) Studies with incomplete or missing data; (4) Studies lacking relevant outcome measures aligned with the objectives of this review.

Data extraction and quality assessment

Two reviewers worked separately to retrieve data using a standardized data collection form created for this review. The following variables made up the extracted data from all of the included studies: author(s) and year of publication, country or study location, study design and sample size, patient characteristics, including age, sex, and histopathological subtype of Renal Cell Carcinoma (RCC), type of claudin protein evaluated and method of detection (immunohistochemistry or other techniques), clinicopathological parameters assessed (e.g., tumor grade, stage, size, capsular invasion, metastasis), survival outcomes reported, including Cancer-Specific Survival (CSS), Disease-Free Survival (DFS), Overall Survival (OS), and Cumulative Survival (CS), main findings, including statistical significance and direction of association between claudin expression and prognostic variables.

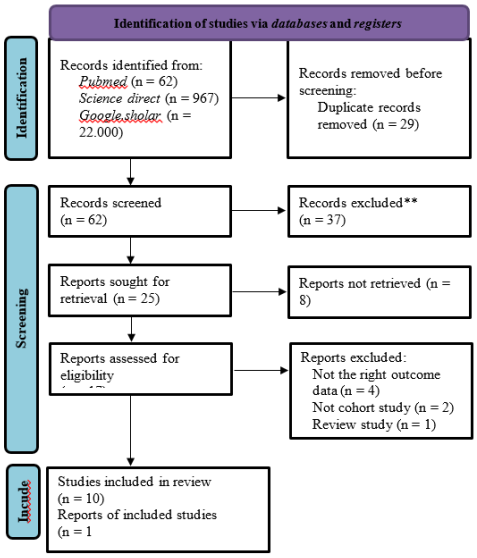

Figure 2. Data collection following PRISMA guidelines

Table 1. Newcastle-Ottawa scale quality assessment on cohort studies

No.	Author (s), year of publication	Selection				Comparability		Outcome			Total score	Overall judgement
		Representativeness of the exposed cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that outcome if interest was not present at start of study	Study controls is for sex and age	Study control is for tumor size and stage	Assessment of outcome	was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts		
1	Erlmeier, 2022	*	-	*	*	*	*	*	*	*	8	low risk
2	Fritzsche, 2008	*	-	*	*	*	*	*	*	*	8	low risk
3	Lechpamer, 2008	*	-	*	*	*	*	*	*		7	low risk
4	Li, 2018	*	-	*	*	*	*	*	*		7	low risk
5	Mikuteit, 2022	*	-	*	*	*	*	*	*	*	8	low risk
6	Onagi, 2024	*	-	*	*	*	*	*	*	*	8	low risk
7	Shin, 2011	*	-	*	*	*	*	*	*		7	low risk
8	Virman, 2014	*	-	*	*	*	*	*	*		7	low risk
9	Yang, 2022	*	-	*	*	*	*	*	*		7	low risk
10	Zhu, 2020	*	-	*	*	*	*	*	*		7	low risk

When two or more reviewers couldn't agree on how to extract data, they discussed it and, if necessary, brought in a third opinion to finalize the process. A non-randomized study-specific tool, the Newcastle-Ottawa Scale (NOS), was used to assess the research's methodological quality and bias risk. Selection, comparability, and evaluation of outcomes were the three pillars upon which each research rested. A clear evaluation of the methodological rigor across studies is provided by summarizing the findings of the quality assessment in a table (table 1).

Results

The initial retrieval yielded 62 studies from databases, and 29 duplicates were removed. After examining the titles and abstracts, the remaining 25 articles were reviewed in full text. Finally, 10 articles were included as being relevant to the subject.

Characteristics of included studies

The included studies originated from seven

countries—Germany, Switzerland, the United States, China, Japan, Korea, and Finland—and were published between 2008 and 2024. All studies involved patients diagnosed with renal cell carcinoma who underwent nephrectomy, either radical or partial. The predominant histopathological subtype was clear cell RCC (ccRCC), comprising 1,633 cases, followed by papillary RCC (432 cases), chromophobe RCC (113 cases), and renal oncocytoma (12 cases). Additionally, three cases were reported with unclassified histological features. A total of 2,192 patients were included across all studies, consisting of 696 females and 1,371 males. All patients were adults, with both the median and mean age exceeding 60 years. Collectively, these data indicate that clear cell RCC remains the predominant histopathological subtype among nephrectomized RCC patients worldwide, reflecting its high prevalence across diverse geographic populations (Table 2).

Table 2. Study characteristics and outcomes of claudin expression in RCC Patients

No	Author(s), Year	Country	Period	Sampel (n)	Sex	Age	Type of RCC	Nuclear grade	Stage	Type of Claudin	Detection Technique	Follow up	Outcome
1	Erlmeier *et al*, 2022	Germany	1996 – 2014	81	F = 23; M = 58	59.8	chRCC	N/S	I = 56; II = 14; III = 8; IV = 3	6	IHC	median 40.5 mo	Overall survival
2	Fritzsche *et al*, 2008	Switzerland	1993 - 2004	318	F = 105; M = 213	≤ 61 = 166; > 61 = 152	ccRCC, pRCC, chRCC	Grade 1* = 39; Grade 2* = 229; Grade 3* = 48; Grade 4* = 2	N/S	1	IHC	0-177 mo (median 99 mo)	Disease spesific survival
3	Lechpamer *et al*, 2008	United States	1999 - 2004	141	F = 82; M = 59	63.3	ccRCC, pRCC, chRCC, Oncocytoma	N/S	N/S	1, 3, 4, 7, 8	IHC	N/S	Cumulative survival
4	Li *et al*, 2018	China	April - September 2012; October - December 2017	534	F = 40; M = 80	Median = 60 (range 49-76); Media = 56 (range 21-86)	ccRCC	Grade 1*** = 41; Grade 2*** = 65; Grade 3*** = 14; Grade 4*** = 0	I = 87; II = 8; III = 23; IV = 2	7	qrt-PCR, western blotting, IHC	N/S	Disease free survival, overall survival

5	Mikuteit *et al*, 2022	Germany	1985 - 2007	368	F = 52; M = 190; N/E = 55	64.5	pRCC	Grade 1*** = 48; Grade 2*** = 125; Grade 3*** = 85; Undetermined = 56	I/II = 140; III/IV = 18	6	IHC	median 29 mo (IQR 18.0-71.8)	Overall survival
6	Onagi *et al*, 2024	Japan	2004 - 2020	165	F = 49; M = 116	< 70 = 102; ≥ 70 = 63	ccRCC	Grade 1* = 19; Grade 2* = 98; Grade 3* = 43; Grade 4* = 4	I = 112; II = 19; III = 21; IV = 13	10	Western blotting, IHC	N/S	Cancer spesific survival
7	Shin *et al*, 2011	Korea	January 2000 - December 2007	119	F = 34; M = 85	55.7 ± 10.7	ccRCC	Grade 1* = 2; Grade 2* = 66; Grade 3* = 37: Grade 4* = 14	N/S	1, 7	IHC	N/S	Cancer spesific survival
8	Virman *et al*, 2014	Finland	1985 - 1995	229	F = 94; M = 135	65	ccRCC, pRCC, chRCC, Unclassified	Grade 1/2*** = 23; Grade 3*** = 115; Grade 4*** = 91	I = 104; II = 29, III = 40; IV = 56	1, 2, 3, 4, 5, 7	IHC	median 48 mo (IQR 1.27-7.24)	Cumulative survival
9	Yang *et al*, 2022	China	N/S	176	F = 31; M = 91	≤ 65 = 77; > 65 = 45	ccRCC	Grade 1*** = 3; Grade 2*** = 36; Grade 3*** = 64; Grade 4*** = 19	I = 21; II = 16; III = 81; IV = 4	10	qrt-PCR, western blotting, IHC	N/S	Disease-free survival, overall survival
10	Zhu *et al*, 2020	China	June 2008 - January 2011	530	F = 186; M =	≤ 60 = 264; > 60 = 266	ccRCC	Grade 1** = 14; Grade 2** = 227; Grade 3** =	I = 265; II = 57; III = 123; IV = 83; Unclass	8	qrt-PCR, western blotting, IHC	N/S	Overall survival

					344			206; Grade 4 = 75; Unclassified = 8	ified = 2				

ccRCC: "clear cell renal cell carcinoma; chRCC: chromophobe renal cell carcinoma; pRCC: papillary renal cell carcinoma; N/A: not applicable; N/S: not stated; F: female; M: male; IHC: immunohistochemistry: qrt-PCR: quantitative rapid analysis-polymerase chain reaction; *: Fuhrman criteria; **: WHO-ISUP criteria; ***: unknown"

Analysis between claudin expression and clinicopathological features

A total of 10 studies were included in this systematic review, all of which investigated the association between *claudin* expression and tumor aggressiveness in Renal Cell Carcinoma (RCC), evaluated through tumor stage, pathological tumor size (pT), lymph node status (pN), distant metastasis (M), and nuclear grade assessed by Fuhrman or ISUP criteria.

Four of the ten studies directly analyzed the correlation between claudin expression and tumour stage, while the remaining six evaluated its correlation with nuclear grade, tumor size, lymph node involvement, or distant metastasis. Among these, three studies demonstrated a significant correlation between claudin expression and tumour stage. The strongest significance correlation was reported by Zhu et al. ($p < 0.01$, Student's *t*-test), followed by Shin et al. ($p = 0.009$, Fisher's exact test) and Onagi et al. ($p = 0.034$, Mann–Whitney test). In contrast, Virman et al. reported no significant correlation ($p = 0.331$, chi-square test). Regarding tumor size (pT), four studies found a significant correlation between claudin expression and tumour size, with Li et al. ($p = 0.001$, chi-square test) and Shin et al. ($p = 0.001$, Fisher's exact test) reporting the highest levels of significance, followed by Yang et al. ($p = 0.002$, Mann–Whitney test) and Zhu et al. ($p < 0.05$, Student's *t*-test). Conversely, three studies—Erlmeier et al. ($p = 0.952$), Mikuteit et al. ($p = 0.717$), and Fritzsche et al. ($p = 0.213$)—showed no statistically significant association.

Four studies evaluated the correlation between claudin expression and lymph node status. Among these, only Fritzsche et al reported a significant correlation ($p = 0.029$, chi-square test), whereas Erlmeier et al. ($p = 1.0$), Mikuteit et al. ($p = 0.674$), and Shin et al. ($p = 1.00$) reported no significant correlation. Six studies investigated the correlation between *claudin* expression and distant organ metastasis. Two studies—Shin et al. ($p = 0.035$, Fisher's exact test) and Zhu et al. ($p = 0.05$, Student's *t*-test)—demonstrated a significant correlation, while four studies—Erlmeier et al. ($p = 1.0$), Fritzsche et al. ($p = 0.073$), Mikuteit et al. ($p = 1.0$ and 0.3272), and Onagi et al. ($p = 0.173$)—did not find any significant correlation. Nine studies evaluated the correlation between *claudin* expression and nuclear grade (according to the Fuhrman or ISUP criteria). Six of these studies reported a statistically significant correlation—Lechpammer et al. ($p = 0.016$), Li et al. ($p = 0.044$), Onagi et al. ($p < 0.001$), Shin et al. ($p = 0.004$), Yang et al. ($p = 0.0296$), and Zhu et al. ($p = 0.05$). The remaining three studies—Erlmeier et al. ($p = 0.925$), Fritzsche et al. ($p = 0.069$), and Mikuteit et al. ($p = 0.615$)—did not find a significant correlation.

Overall, most studies demonstrated that the alterations in claudin expression were significantly correlated with one or more indicators of tumour aggressiveness, particularly tumour stage, size, and nuclear grade, supporting its potential role as a molecular prognostic marker in renal cell carcinoma.

Analysis between claudin expression and cancer-specific survival

Three research investigated renal cell carcinoma patients' claudin expression and its association with Cancer-Specific Survival (CSS). Fritzsche et al. (2008) and Onagi et al. (2024) both found a statistically significant correlation between claudin expression and worse CSS (p = 0.008, Kaplan-Meier log-rank test and p = 0.0029, Kaplan-Meier log-rank test, respectively). In contrast, Shin et al. (2011) reported no significant correlation ($p = 0.110$ and $p = 0.662$, Kaplan–Meier log-rank test). The follow-up period used across these studies varied; Fritzsche et al. applied a 3-year follow-up, Onagi et al. a 10-year follow-up, and Shin et al. a 140-month follow-up.

Patients with renal cell carcinoma were found to have a significantly lower disease-specific survival rate when their claudin expression was elevated or aberrant, according to multivariate Cox regression analyses conducted by Fritzsche et al. and Onagi et al.

Analysis between claudin expression and disease-specific survival

Of the 10 studies that looked at renal cell carcinoma patients, two found a link between claudin expression and disease-specific survival (DSS). Li et al. (2018) reported a *p*-value of <0.0001 using the Kaplan–Meier log-rank test, while Yang et al. (2022) also found a highly significant correlation with a *p*-value of <0.0001 using the same statistical method. The follow-up period varied between the two studies: Li et al. applied a 56-month follow-up, whereas Yang et al. applied a 120-month follow-up. Both studies further evaluated the prognostic value of claudin expression using multivariate Cox regression analysis, confirming that aberrant claudin expression was independently associated with poorer disease-free survival outcomes.

Analysis between claudin expression and overall survival

Five of ten studies evaluated the correlation between claudin expression and Overall Survival (OS) in patients with renal cell carcinoma. Among these, three studies reported a statistically significant correlation, while two found none. The studies demonstrating a significant correlation were conducted by Li et al. (2018) (p = 0.024, Kaplan–Meier log-rank test), Yang et al. (2022) (p < 0.0001, Kaplan–Meier log-rank test), and Zhu et al. (2020) (p < 0.0001, Kaplan–Meier log-rank test). The follow-up period varied across studies; Li et al. applied a 56-month follow-up, Yang et al. applied a 120-month follow-up, and Zhu et al. applied an 80-month follow-up. In contrast, Erlmeier et al. (2023) (p = 0.174, Kaplan–Meier log-rank test) and Mikuteit et al. (2022) (p = 0.660 and 0.174, Kaplan–Meier log-rank test) reported no statistically significant correlation between claudin expression and OS. The follow-up period varied among studies; Erlmeier et al. applied a 5-year follow-up, and Mikuteit et al. applied a 250-month follow-up. Furthermore, Yang et al. (2022) and Zhu et al. (2020) evaluate the prognostic value of claudin expression using multivariate Cox regression analyses, both of which confirmed that altered claudin expression was independently correlated with decreased overall survival.

Analysis between claudin expression and cumulative survival

Two out of ten studies evaluated the correlation between claudin expression and cumulative survival in patients with Renal Cell Carcinoma (RCC). Among these, one study reported a statistically significant correlation, whereas the other study reported no significant correlation. The study conducted by Lechpammer et al. (2008) showed a significant correlation between claudin expression and cumulative survival, with *p*-values of 0.038 and 0.031 (Kaplan–Meier log-rank test). In contrast, Virman et al. (2014) reported no significant correlation, although no *p*-value was provided; survival analysis in that study was performed using the Kaplan–Meier log-rank test.

Table 3. Summary of Claudin–Clinicopathological and prognostic correlations in RCC studies

No.	Author(s), year	Claudin Correlation with Histopathological Feature	Claudin Correlation with Outcome
1	Erlmeier *et al*, 2022	Increased claudin-6 expression is not associated with poorer histopathological features	Increased claudin-6 expression is not associated with worse OS in chRCC
2	Fritzsche *et al*, 2008	Increased claudin-1 expression is associated with worse histopathological features in both ccRCC and pRCC	Increased claudin-1 expression is associated with poorer CSS in ccRCC but not associated with pRCC
3	Lechpamer *et al*, 2008	Increased claudin-3 expression correlated with higher nuclear grade at ccRCC	Increased claudin-3 and claudin-4 expression was not correlated with worse CS in ccRCC

4	Li *et al*, 2018	Increased claudin-7 expression correlated with high nuclear grade at ccRCC	Increased claudin-7 expression was correlated with better DFS and OS in ccRCC
5	Mikuteit *et al*, 2022	Increased claudin-6 expression was not correlated with worse histopathological features in pRCC	Increased claudin-6 expression was not correlated with worse OS in pRCC
6	Onagi *et al*, 2024	Increased claudin-10 expression correlated with worse histopathological features in ccRCC	Increased claudin-10 expression correlated with worse CSS in ccRCC
7	Shin *et al*, 2011	Nuclear grade, tumor size, and distant organ metastases were all connected with greater claudin-1 expression in ccRCC, while lymph node metastasis was not. On the other hand, higher nuclear grade was correlated with increased claudin-7 expression, but TNM stage was not.	Increased claudin1 expression correlated with worse CSS on ccRCC, whereas increased claudin7 expression was not correlated with worse CSS
8	Virman *et al*, 2014	Decreased claudin-1, -2, and -4 expression correlated with higher nuclear grades in ccRCC, while increased claudin-3, -5, -7 expression correlated with worse histopathological features	Increased claudin-1 and -2 was not correlated with worse CS in ccRCC
9	Yang *et al*, 2022	Increased claudin-10 expression correlated with smaller tumor size and lower nuclear grade in ccRCC	Increased claudin-10 expression correlated with better DFS and OS in ccRCC
10	Zhu *et al*, 2020	Decreased claudin-8 expression correlated with worse histopathology features in ccRCC	Increased claudin-8 expression correlated with better OS on ccRCC

"ccRCC: clear cell renal cell carcinoma; chRCC: chromophobe renal cell carcinoma; pRCC: papillary renal cell carcinoma; CSS: cancer-specific survival; DFS: disease-free survival; OS: overall survival; CS: cumulative survival"

Discussion

The Von Hippel-Lindau (VHL) gene is an important gatekeeper in renal epithelial cells and a classical tumor suppressor. This gene's protein is crucial for controlling hypoxia-inducible factors (HIFs), which is why abnormal angiogenic signaling and other cancer-causing traits are linked to VHL deficiency. The conventional purpose of VHL is to degrade HIF, however it also regulates RNA polymerase II, atypical protein kinase C, cellular senescence, extracellular matrix construction, microtubule stability, and other activities that do not include HIF. The importance of VHL in the early phases of cancer transformation is highlighted by its role in maintaining E-cadherin-mediated adherens junctions via HIF activation (Harten et al., 2009).

The concept that VHL failure leads to a dedifferentiated phenotype in renal tubular epithelial cells is further supported by VHL's involvement in maintaining tight junction integrity. This approach creates a paradox—while VHL is genetically a tumor suppressor, its absence appears to have a limited influence on renal epithelial proliferation. A compelling hypothesis is that dedifferentiation may empower renal epithelial cells to tolerate otherwise lethal genetic alterations that would typically trigger apoptosis. The VHL status significantly impacts the expression of occludin and claudin, via transcriptional regulation at the mRNA level. Restoring occludin and claudin expression increases the tight junction assembly by re-establishing their connection with zonula occludens-1 (ZO-1). In line with the severe phenotype seen when claudin is disrupted, re-expression of claudin has a greater effect than occludin among them (Harten et al., 2009).

In renal cell carcinoma, activation of the HIF signaling pathway may alter tight junction dynamics. In RCC cells expressing the type IIC VHL mutant, epithelial morphology and tight junction formation were reinstated, showing the HIF's involvement in these processes. In contrast, HIF knockdown using siRNA

did not preserve tight junction integrity, suggesting that both HIF-dependent and HIF-independent pathways may play a role in cellular dedifferentiation and junctional disorganization. Dysregulated VHL function affects differentiation and formation of the tight junction through various mechanisms, potentially presenting new therapeutic strategies to inhibit the tumorigenesis of clear cell renal cell carcinoma.

In VHL-defective ccRCC, transcriptional repressors such as SNAIL1, ZEB2, and E47 are upregulated, contributing to epithelial–mesenchymal transition (EMT). HIF has been shown to bind promoter regions of Twist in hypopharyngeal and lung carcinoma cells, and SNAIL1 in ovarian cancer cells, the latter via a Notch-dependent mechanism. In VHL-deficient RCC, tight junction assembly is likely disrupted by HIF-mediated regulation of SNAIL1. Histone deacetylase (HDAC) inhibitors, such as sodium butyrate, downregulated the HIF activation and promoted epithelial morphology restoration, tight junction reassembly, and increased expression of E-cadherin, occludin, and claudin-1. Sodium butyrate selectively decreases HIF-1 rather than HIF-2 protein levels, consistent with findings indicating that HIF-1 plays a more dominant role in mediating EMT in VHL-dysregulated ccRCC. HDAC inhibitors may exert these effects not only through HIF repression but also by modulating other transcriptional regulators, including SNAIL1, and have been shown to inhibit TGF-β–induced EMT in renal tubular cells (Harten et al., 2009).

Claudin expression facilitates ccRCC progression at the molecular level by forming complexes with the L-type amino acid transporter 1 (LAT1). This interaction stimulates the mTOR signaling pathway and its downstream targets, including MYC and glycolysis-related genes, thereby enhancing tumor cell proliferation, survival, and invasiveness (Onagi et al., 2024).

Antitumor immune responses are influenced by downregulation of key immunomodulatory molecules, including the major histocompatibility complex (MHC), chemokines, and their receptors. A particular subtype of claudin, the claudin-low cluster, promotes this downregulation. The heterogeneity of antigen-presenting cells (APCs), CD4+ T cells, Th22 cells, monocytes, regulatory T cells, dendritic cells, eosinophils, and basophils contributes to weakened immune-mediated cytotoxicity. Distinct features in tumor-infiltrating immune cells (TIICs)—including B cells, macrophages, and CD4+ T cells—also modulate immune surveillance and tumor progression (Zhang et al., 2022).

Claudin overexpression inhibits migration and invasion in ccRCC cells, although it simultaneously reduces their wound-healing capacity. Mechanistically, this is associated with downregulation of N-cadherin and vimentin expression, alongside upregulation of E-cadherin, suggesting a partial mesenchymal-to-epithelial transition. Claudin overexpression also inhibits ccRCC cell proliferation by significantly suppressing the AKT signaling pathway, further highlighting its potential role as a context-dependent regulator of tumor behavior (Zhu et al., 2020).

Alterations in claudin expression in Renal Cell Carcinoma (RCC) are facilitated by multiple interconnected mechanisms, encompassing genetic and epigenetic regulation, signaling pathway dysregulation, microenvironmental remodeling, post-translational modifications, and Epithelial-To-Mesenchymal Transition (EMT).

1. Genetic and Epigenetic Factors

Transcriptional regulation of claudin is significantly impacted by mutations and inactivations of tumor suppressor genes such VHL, PBRM1, and SETD2. Renal epithelial cells undergo a persistent hypoxic condition when hypoxia-inducible factor-1α (HIF-1α) builds up due to the loss of VHL function. Chronic hypoxia subsequently modifies the expression of multiple membrane-associated proteins, including claudins (Amin et al., 2022; Hsieh et al., 2017). DNA methylation and histone modification have been implicated in the epigenetic control of claudin expression (Singh & Dhawan, 2015).

2. Dysregulation of intracellular signaling pathways

Hyperactivation of the PI3K/AKT/mTOR and

MAPK/ERK signaling cascades enhances claudin expression, inducing tumor cell proliferation and capsular invasion in RCC (Onagi et al., 2024). On the other hand, decreasing claudin expression is achieved by the promotion of Epithelial-To-Mesenchymal Transition (EMT) when the TGF-β pathway is activated. Tumor cells are able to migrate, invade, and metastasize further when claudin is downregulated, which compromises tight junction integrity (Wang et al., 2022).

3. Tumor microenvironmental changes

Mutations or functional loss of VHL induce chronic intracellular hypoxia, which promotes the expression of pro-angiogenic factors such As Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMPs). These molecular alterations compromise claudin stability at the cell membrane by reducing its expression or altering its subcellular localization (Monjaras-Avila et al., 2023). In addition, inflammatory cytokines like IL-6 and TNF-α have been shown to interfere with the structure of tight junctions, reduce the expression of claudin, and encourage tumors to grow invasively (Ding et al., 2013).

4. Post-Translational Modifications (PTMs)

Claudins undergo multiple PTMs, including phosphorylation, ubiquitination, and palmitoylation, which collectively influence their stability and membrane localization. Protein kinase C (PKC)-mediated phosphorylation may induce claudin internalization from the plasma membrane, resulting in reduced immunohistochemical detection and functional impairment of tight junctions (Ding et al., 2013).

5. Epithelial-to-Mesenchymal Transition (EMT)

Enhanced motility and invasiveness are hallmarks of the mesenchymal phenotype, which epithelial cells acquire during EMT by losing their polarity and intercellular adhesion. This transition is accompanied by decreased expression of specific claudin isoforms (e.g., claudin-1, -2, -4, and -7) and increased expression of claudin-10, which promotes tumor invasiveness (Wang et al., 2022).

Cell-surface claudin expression also facilitates Clear Cell Renal Cell Carcinoma (ccRCC) progression by forming complexes with the L-type amino acid transporter 1 (LAT1). LAT1 activates the mTOR signaling cascade and its downstream targets, including MYC and glycolytic genes, thereby enhancing tumor proliferation, survival, and invasiveness. Overexpression of LAT1 has been correlated with poor clinical outcomes and reduced overall survival in RCC patients (Onagi et al., 2024).

LAT1 plays a critical role in the transport of essential amino acids and interacts with CD98, a key cofactor required for its transport activity. The LAT1–CD98 interaction enhances mTOR pathway activation. CD98 and claudin share overlapping hydrophobic binding residues on LAT1, suggesting that claudin and CD98 compete for LAT1 binding, potentially influencing downstream oncogenic signaling (Onagi et al., 2024).

Downregulation of claudin in RCC also affects the expression of transforming growth factor-β (TGF-β), a major EMT inducer. Normally, claudins suppress TGF-β expression and act as negative regulators of EMT signaling driven by TGF-β1 and Musashi-2. Conversely, claudin overexpression has been shown to inhibit invasion in colorectal and lung carcinoma through modulation of the EMT and MAPK pathways. Furthermore, EMT itself contributes to chemotherapeutic resistance, whereas claudin upregulation has been associated with enhanced chemosensitivity through caspase pathway activation in lung carcinoma (Li et al., 2018).

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General

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Approval

There was no original data gathering or contact with human or animal participants in this systematic review; instead, it relied on previously published literature. Ethical clearance and informed consent were unnecessary since the study followed all applicable national and international regulations.

In order to guarantee methodological openness and reproducibility, the writers developed the review methodology according tao the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. The authors registered the review protocol in an open-access database (PROSPERO) prior to data extraction and analysis.

Conflict of interest

The authors declare that no financial support was received for this study.

Ethical declaration

The data presented here are the results of a systematic review. There was no need for ethical clearance since no human volunteers were involved in the original data gathering. Following the PRISMA 2020 criteria, the review was conducted.

Authors contribution

ZN: conceptual idea, data finding, data extraction, funding, analysing, drafting, evaluating. GM: conceptualization, integrating data, analysing, evaluating. AN: conceptualization, integrating data, analysing, evaluating.

Data availability

Comprehensive details regarding the original contributions of this work are contained herein or in the supplementary documentation. For further clarification, please reach out to the corresponding authors.

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