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ORIGINAL ARTICLE

CD68- and CD163-Positive Tumor-Associated Macrophages in Renal Clear Cell Carcinoma

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Abstract

Background: This study aimed to analyze the infiltration of tumor-associated macrophages (TAMs) in clear cell renal cell carcinoma (ccRCC) and to assess their prognostic significance.

Methods: This study involved a cohort of 106 patients with ccRCC who underwent partial or radical nephrectomy. Immunohistochemistry (IHC) was employed to assess the expression of two distinct types of macrophages at various tissue locations. The diagnostic utility of CD68-positive ($CD68^+$) and CD163-positive ($CD163^+$) macrophages was determined via receiver operating characteristic (ROC) curves.

Results: Compared with those in adjacent tissues, the numbers of $CD68^+$ and $CD163^+$ TAMs were significantly elevated in ccRCC tissues. ROC curve analysis revealed that the area under the curve (AUC) for CD68 was 0.782 and that the AUC for CD163 was 0.879, indicating that these factors are statistically significant for the diagnosis of ccRCC ($P = 0.01$). Patients with high expression of CD68/CD163 in cancer tissues exhibited shorter overall survival (OS) ($P < 0.01$). Patients with a low density of both intracellular $CD68^+$ and $CD163^+$ TAMs experienced a more favorable prognosis ($P < 0.01$).

Conclusions: TAMs, particularly the M2 subtype ($CD163^+$), are identified as adverse prognostic factors for ccRCC patients. Those with a high density of M2 macrophages tend to have a poorer prognosis.

Keywords: renal clear cell carcinoma, tumor-associated macrophages, CD68, CD163, cellular immunity

Introduction

Renal cell carcinoma (RCC) encompasses a spectrum of malignant carcinomas originating from nephrons, with clear cell renal cell carcinoma (ccRCC) being the most common type, constituting approximately 75% of cases. The management of ccRCC has garnered significant attention, with increasing evidence suggesting that the immune response plays a pivotal role in the carcinogenesis of ccRCC and its response to therapy .

Macrophages are potent immune effector cells with remarkable functional adaptability, which has sparked significant interest in exploring their role in cancer immunotherapy. Specifically, the diverse functions of macrophages, both antitumor and protumor, depending on the context, have prompted investigations into their therapeutic potential. Tumor-associated macrophages (TAM) are defined as macrophages located within or in close proximity to the tumor. Macrophages typically exhibit two distinct polarization states: the M1 phenotype, which is known for its proinflammatory and antitumor properties, and the M2 phenotype, which is associated with promoting tumor progression and metastasis.

CD68 is a widely recognized marker for macrophages, whereas CD163 serves as a specific marker for M2-type macrophages. In this study, we employed immunohistochemistry (IHC) to assess the distribution and density of $CD68^+$ and $CD163^+$ macrophages in various regions of tumor tissues from patients with ccRCC.

Our goal was to investigate the potential prognostic significance of these markers in postoperative ccRCC patients, providing insights for clinical application.

1. Methods and Materials

2.1 Patients

We consecutively collected 366 patients diagnosed with ccRCC who underwent surgery at the Department of Urology, Yantai Yuhuangding Hospital of Qingdao University, between January 2015 and December 2017. The inclusion criteria for patients were as follows: (1) aged 18 years and older, provided informed consent, and voluntarily participated in this study; (2) compliant with the 2010 EAU Guidelines for Renal Cell Carcinoma; (3) had not received any preoperative antitumor therapies such as radiofrequency ablation, chemotherapy or radiation therapy; (4) had undergone either partial nephrectomy or radical nephrectomy, with confirmation by two or more pathologists that the surgical specimens exhibited clean-cut margins and were free from residual ccRCC. The exclusion criteria were as follows: (1) patients with recent infectious diseases or a history of autoimmune diseases or infectious diseases; (2) patients with a history of primary tumors in other organs; (3) patients who had undergone preoperative radiotherapy or chemotherapy; and (4) Individuals whose laboratory and pathology data were incomplete. Following a rigorous screening process, a total of 106 ccRCC patients who met the criteria were included in this study. Informed consent was obtained and signed by all participating subjects. Additionally, the study was approved by the Ethics Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University.

2.2 Data collection

After providing informed consent, we conducted face-to-face interviews with the patients. For data collection, we employed the ccRCC Patient Questionnaire (see Appendix I), which was designed by our research team. This questionnaire encompasses a range of inquiries covering general demographic data, health-related details such as smoking and alcohol consumption, medical history, medication history, and various parameters related to the disease, including imaging data, laboratory indicators, surgical information, and pathology reports. During the follow-up period, we recorded a comprehensive set of data, which included various essential parameters, including tumor size (cm), clinical T stage, pathological grade, metastasis, serum creatinine (Scr), and the glomerular filtration rate (GFR). Our follow-up strategy involved rigorous monitoring of patient health. Post surgery, the first follow-up occurred every three months during the initial two years, followed by biannual follow-ups for the subsequent two years and, finally annual check-ups in the previous year. These follow-up sessions included a detailed medical history, physical examination, laboratory blood tests, imaging assessments, and cases of patient fatality, which were obtained through telephone interviews. The follow-up period was until January 10, 2022.

2.3 IHC staining of tissue samples

Tissue samples were collected from both the tumor and adjacent nontumor areas of the included patients. These excised samples were promptly preserved in liquid nitrogen and subsequently transferred to a -80°C refrigerator. For further analysis, we performed H&E staining. The primary antibodies used were anti-CD68 rabbit monoclonal antibody (dilution 1:500) (Absin, China) and anti-CD163 rabbit monoclonal antibody (1:500) (Absin, China), and the secondary antibody used was goat anti-rabbit IgG (1:500) (Absin, China). After staining, we employed the hot spot quantitative counting method to assess $CD68^+$ TAMs and $CD163^+$ TAMs. Each sample was initially observed at low magnification (100×), and five regions with the highest counts of positively stained cells, known as hotspots, were selected. The number of macrophages within the five hotspot areas was counted, and the average value was determined at high magnification (400×). The tumor stroma (TS) and tumor nest (TN) were counted separately. In this study, TS was defined as the stromal tissue surrounding the tumor, whereas TN was defined as the tumor tissue itself. Statistical analysis categorized these counts into lower and

higher groups using the median values as cutoff points. All the results were evaluated independently by two pathologists, who were blinded to the patients' clinical information.

2.4 Statistics

Spearman's Rho and χ^2 tests were employed to compare the expression levels of CD68 and CD163 with patient and tumor characteristics. Kaplan–Meier analysis, along with log-rank tests, was used to determine differences in overall survival (OS) based on CD163 and CD68 expression. Additionally, we utilized Cox regression proportional hazards models to estimate hazard ratios (HRs) for death, considering both uni- and multivariate analyses. Covariates with a p value ≤ 0.05 in the univariate analysis were included in the multivariate analysis. All the statistical tests were two-sided, and significance was determined at $p \leq 0.05$. The statistical analyses were performed via IBM SPSS Statistics 25 (IBM, Armonk, NY, USA).

2. Results

We measured the expression levels of CD68 and CD163 in both the TSs and TNs of all 106 samples. Our analysis revealed the presence of $CD68^+$ (Figure 1a, b) and $CD163^+$ (Figure 1c, d) macrophages in both the TS and TN of the TNC. The relationships between TAM density ($CD68^+$ or $CD163^+$) and clinicopathological features are presented in Table 1. The cutoff values were as follows: 16.3 for CD68 in the TS, 26.2 for CD68 in the TN, 16.6 for CD163 in the TS, and 23.0 for CD163 in the TN. Additionally, for the CD163/CD68 ratios, the cutoff values were 0.91 for TN and 0.94 for TS. (Table 2). Our research revealed significant correlations between high CD68+ TAM density in both the TS and TN and several clinical factors. Notably, it was significantly correlated with larger tumor size (p<0.001). Furthermore, the high density of $CD163^+$ TAMs in TS patients was significantly correlated with older age (p=0.031), although this correlation was not observed in TNs (p=0.310). In addition, both high $CD68^+$ TAM and $CD163^+$ TAM densities in the TS and TN were associated with higher histological grade (p<0.001), larger tumor size (p<0.001), and lymph node metastasis (p<0.001). Conversely, no significant correlation was observed between the number of TAMs ($CD68^+$ or $CD163^+$ cells and the CD163/CD68 ratio) and patient sex in the TS or TN. However, the CD163/CD68 ratio in TS patients was correlated with patient age (p=0.012) and tumor size (p=0.012). No such correlations were found with other clinical and pathological features. We further conducted univariate and multivariate Cox regression analyses to examine the impact of clinicopathological prognostic factors and the expression of CD68 and CD163 on OS (Table 3). Multivariate Cox regression analysis revealed that CD163+ TAMs in the TS and TN were strongly correlated with patient OS (HR=7.22, 95% CI 1.06–25.54, p=0.003; HR=3.56, 95% CI 1.03–15.56, p=0.045). K–M analysis and the log-rank test were used to compare the expression status and survival rates associated with different TAMs. A higher density of CD68+ TAMs in the TN was not correlated with OS (p=0.819). However, a greater density of CD163+ TAMs in the TN was significantly correlated with OS (p=0.006), whereas a greater $CD68^+/CD163^+$ ratio in the TN was not correlated with OS (p=0.084) (Figure 2a, c, e). In TS, a greater density of CD68+ TAMs in the TS was not correlated with OS (p=0.433), whereas a greater density of CD163+ TAMs in the TS was significantly correlated with OS (p=0.043). Similarly, a higher $CD68^+/CD163^+$ ratio in the TS was not correlated with OS (p=0.738) (Figure 2b, d, f).

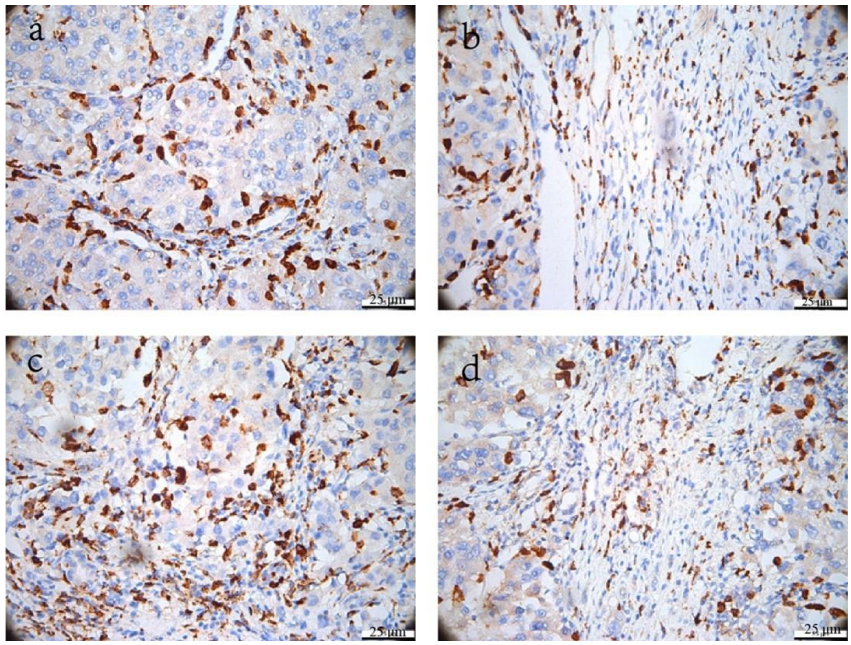

Figure 1. Immunohistochemical staining of CD68+ tumor-associated macrophages (TAMs) and CD163+ tumor-associated macrophages (TAMs) in ccRCC. Representative images of high-density CD68+ staining (a, b) and CD163+ staining (c, d) in the tumor stroma and tumor nest. (Original magnification, ×200).

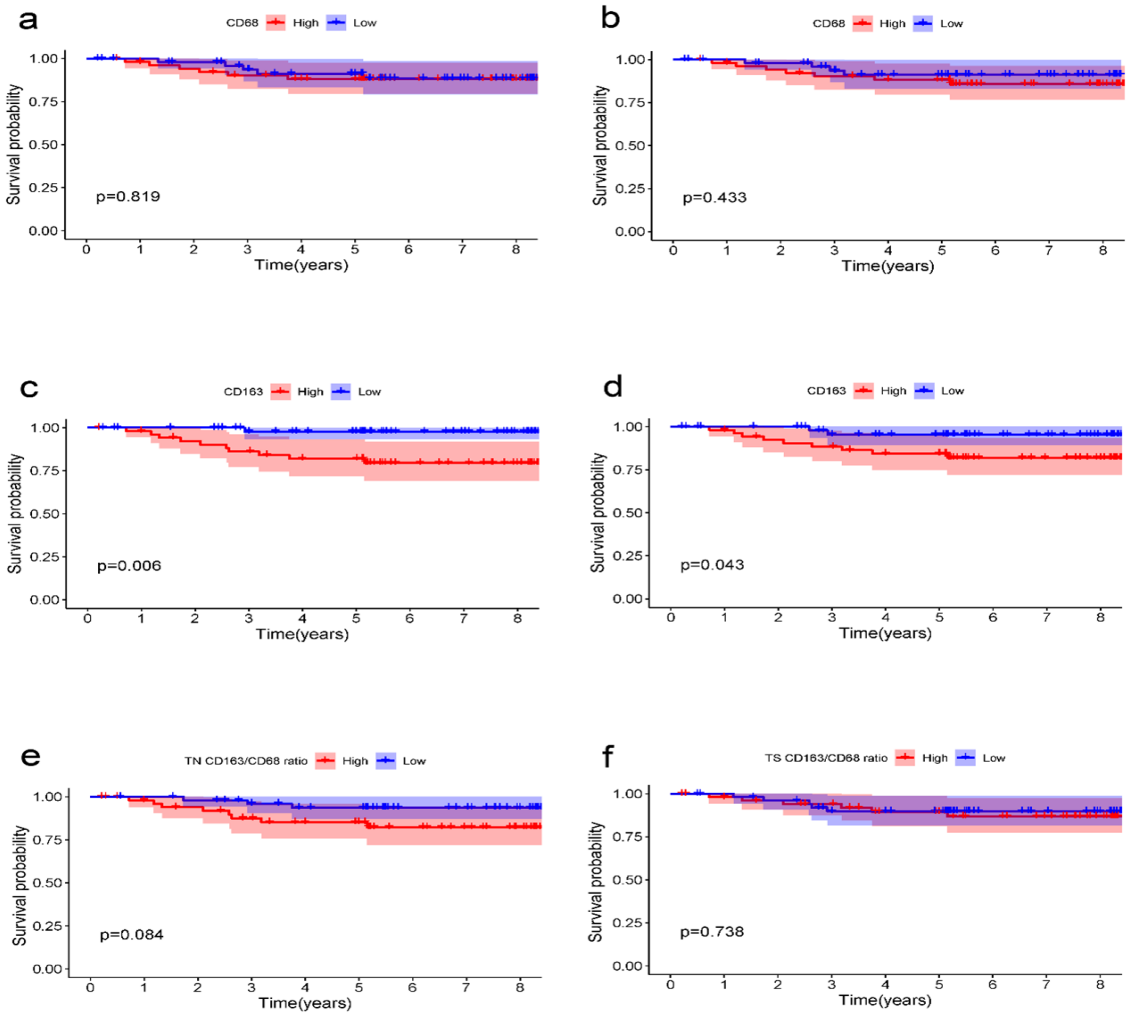

Figure 2. Prognostic significance of TAMs in breast cancer. The Kaplan–Meier curves for overall survival (OS) were stratified by the median values as the cutoff for prognostic evaluation and divided

into low- or high-TAM variable subsets. CD68+ TAMs did not demonstrate prognostic significance for OS (a, b) in the tumor stroma (TS) or tumor nest (TN). A high density of CD163+ TAMs in the TS and TN was associated with poor RFS and OS (c, d). OS (e, f) curves according to the infiltration density of the CD163+/CD68+ ratio in TSs and TNs.

Table 1. Clinicopathological features of ccRCC and the status of TAMs.

Variables	Mean	SD	Median	Range
CD68+ TAM Tumor nest	31.55	18.84	26.2	8.8-117.2
Tumor stroma	21.13	11.27	16.3	5.6-57
CD163+ TAM Tumor nest	28.49	17.76	23.0	4.8-95
Tumor stroma	18.53	10.01	16.6	2.6-54.4
Ratio of CD163 and CD68 Tumor nest	0.92	0.26	0.91	0.32-1.68
Tumor stroma	0.95	0.21	0.94	0.52-1.49

Table 2. Distribution pattern of TAMs in ccRCC. (*TAMs*, tumor-associated macrophages; *ccRCC*, clear cell renal cell carcinoma; *SE*, standard error)

Clinicopathological features		CD68					CD163						CD163/CD68					
		Tumor nest			Tumor stroma			Tumor nest			Tumor stroma			Tumor nest			Tumor stroma	
	Low	High	*P* value	Low	High	*P* value	Low	High	*P* value	Low	High	*P* value	Low	High	*P* value	Low	High	*P* value
Age (years)			< **0.001**			< **0.001**			**0.031**			0.310			**0.011**			0.121
≤63	23	31		18	36		24	30		25	29		21	33		23	31	
> 63	42	10		45	7		34	18		19	33		33	19		30	22	
Tumor size (cm)			< **0.001**			< **0.001**			< **0.001**			< **0.001**			**0.012**			0.501
≤5	53	4		46	11		55	2		47	10		36	21		30	27	
> 5	12	37		12	37		9	40		10	39		19	30		29	20	
Histological grade			< **0.001**			< **0.001**			< **0.001**			< **0.001**			0.195			0.320
I-II	54	24		52	26		53	25		54	24		39	39		42	36	
III-IV	11	17		1	27		2	26		1	27		10	18		12	16	
Gender			0.821			0.239			0.349			0.368			0.084			0.449
Male	43	28		36	35		42	29		36	35		34	37		35	36	
Female	22	13		22	13		24	11		21	14		23	12		20	15	
Mortality			0.054			0.135			**0.003**			**0.014**			0.166			0.166
No	63	36		57	42		69	30		6	38		5	44		55	44	

										1			5					
Yes	2	5		2	5		1	6		1	6		2	5		2	5	
Lymph node metastasis			**0.001**			**0.034**			**0.009**			**0.006**			0.132			0.642
No	64	33		57	40		64	33		57	40		50	47		51	46	
Yes	1	8		2	7		2	7		1	8		7	2		4	5	

Table 3. Univariate and multivariate Cox regression analyses for overall survival (OS) in patients with ccRCC. (*OS*, overall survival. HR hazard ratio, *CI* confidence interval, *TS* tumor stroma, *TN* tumor nest, **p* value is significant)

Clinicopathological features	Univariate analysis		Multivariate analysis	
	OS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
Age (≤63 vs. > 63)	3.66 (0.38-5.28)	0.260		
Tumor size (≤5cm vs. > 5cm)	3.99 (0.41-8.39)	0.231		
Histological grade (I-II vs. III-IV)	2.89 (0.32-4.30)	0.990		
Gender (Male vs. Female)	1.05 (0. 61-7.91)	0.965		
Lymph node metastasis (No vs. Yes)	4.62 (1. 41-7.27)	0.982		
TN CD68 (low vs. high)	3.21 (0.11-21.64)	0.416		
TS CD68 (low vs. high)	4.33 (0.33-65.47)	0.752		
TN CD163 (low vs. high)	7.57 (1.83-28.80)	**0.035**	7.21 (1.05-25.54)	**0.037**
TS CD163 (low vs. high)	3.78 (1.13-16.47)	**0.041**	3.55 (1.03-15.55)	**0.045**
TN CD163/CD68 (low vs. high)	3.02 (0.11-13.33)	0.135		
TS CD163/CD68 (low vs. high)	0.99 (0.10-3.38)	0.755		

4. Discussion

As crucial components of innate immunity, macrophages, which are known to infiltrate tumor tissues, adapt their function on the basis of specific tumor microenvironments. This adaptation leads to different polarization states, where macrophages can assume distinct roles depending on their polarization type. Specifically, TAMs are macrophages found within or near tumor tissues and are known to polarize into two subgroups: the M1 phenotype and the M2 phenotype. To distinguish and study these macrophage subtypes, CD68 serves as a universal marker of macrophages, whereas CD163 can be used to identify M2-type macrophages. In this study, we explored the relationship between macrophages and ccRCC. We analyzed data from 106 patients who had undergone surgical treatment for ccRCC. Using immunohistochemistry, we assessed the distribution and density of CD68+ and $CD163^+$ macrophages within various regions of ccRCC tumor tissues. Furthermore, we conducted survival analysis to better understand the implications of the presence of macrophages in ccRCC.

In this study, we observed that both intra- and paraneoplastic tissues contained a greater number of $CD68^+$ macrophages than $CD163^+$ macrophages. Additionally, there was a significant positive correlation between the quantity of $CD68^+$ macrophages and the number of $CD163^+$ macrophages in both renal cancer tissues and the tumor stroma. This correlation

aligns with the well-established fact that the total population of macrophages is more abundant than M2-like macrophages are, and CD163 serves as a specific marker for the latter. Through data analysis, we found that macrophage infiltration was notably greater within cancerous tissue. Consequently, CD68/CD163 expression levels are significantly elevated in cancer tissues compared with those in the tumor stroma. This finding is consistent with several recent preclinical studies in various solid tumors (pancreatic, breast, ovarian, gastric, bladder, ovarian, and thyroid cancers). These studies have consistently demonstrated the tumor-promoting function of TAMs. Notably, some researchers have proposed different results from ours. For example, Ren *et al*. reported that CD68 expression in hepatocellular carcinoma tissues was greater than that in paraneoplastic tissues and was associated with lymph node metastasis and the pathological stage of liver cancer tissues. This variance in findings might be attributed to the heterogeneous nature of macrophages in hepatocellular carcinoma, including the presence of Kupffer cells. Additionally, differences in study methodologies, sample types, or clinicopathological characteristics of patients could contribute to these discrepancies .

In our study, we selected three key indicators: $CD68^+$ TAMs, $CD163^+$ TAMs, and the CD163/CD68 ratio. When univariate prognostic analysis was conducted, we found a significant correlation between $CD163^+$ TAMs in cancer tissue and postoperative OS. Specifically, patients with lower $CD163^+$ TAM density tended to have a better prognosis. However, no significant correlations were detected between $CD68^+$ TAMs and the CD68/CD163 ratio. These findings suggest that the M2 subtype of macrophages within TAMs predominantly affects patient prognosis. Furthermore, the M2 subtype of macrophages, which serves as a risk factor, has substantial prognostic value in this context.

In current clinical applications of macrophage immunotherapy models, the primary strategies focus on either reducing TAMs or transforming TAMs from the M2 tumor-promoting phenotype to the M1 antitumor phenotype. One promising approach involves the use of CSF-1R inhibitors that specifically target TAMs. These inhibitors have demonstrated their ability to impede malignant progression. Several selective CSF-1R (or M-CSF) inhibitors are currently undergoing clinical studies. These inhibitors include antibody drugs such as axatilimab, emactuzumab, and cabiralizumab, as well as small-molecule drugs such as pimicotinib, vimseltinib, and evicotinib. They function by blocking CSF-1 signaling, leading to a reduction in TAMs, which in turn has shown promise in improving patient prognosis.

Many studies have shown that increased CD163 expression is associated with increased proliferation and metastatic potential in various solid tumors . Our IHC results and data analysis align with this trend, suggesting that the prognostic impact of TAM density primarily hinges on M2-subtype macrophages. These findings underscore the significant prognostic relevance of M2 macrophages in ccRCC. However, leveraging TAMs for therapeutic purposes presents a challenge because of their widespread distribution in the body and their key role in innate immunity. Achieving specific targeting of M2 TAMs has remained a formidable research hurdle. Currently, clinical therapies targeting M2 TAMs are limited and predominantly focus on CD163. A notable breakthrough has been made by Professor Dongfang Zhou's team, who devised and synthesized a hemoglobin-poly(ε-caprolactone) (Hb-PCL)-conjugated polymer. This innovative compound selectively targets M2 macrophages via CD163 surface receptors. It has demonstrated efficacy in inhibiting tumor metastasis and recurrence and significantly reduces the toxicity associated with small molecule drugs. This was observed in both a murine breast cancer metastasis model (4T1) and a postoperative recurrence model of subcutaneous murine colon cancer (CT26). Additionally, itaconic acid and its derivative Octyl Itaconate have been found to block M2 polarization by inhibiting the JAK1/STAT6 signaling pathway downstream of IL-4. Furthermore, by directly targeting JAK1, itaconic acid and OI have been identified as JAK1 inhibitors. They hold promise for the treatment of type 2 immune-mediated diseases, including allergies, asthma and fibrosis. Moreover, Peng *et al*. highlighted the potential of miR-136 to inhibit M2 macrophage polarization by suppressing CD163 transcription. These developments in tumor immunomodulation hold great promise . While our study provides valuable insights, it has

certain limitations. First, our study was a single-center study with a relatively small sample size, potentially limiting its generalizability. Second, owing to the limited number of disease-specific deaths, our analysis focused primarily on the last five years, with OS as the primary endpoint. Further long-term follow-up is warranted to gain a more comprehensive understanding.

5. Conclusion

Our study sought to examine the prognostic value of TAMs in ccRCC. These findings indicate that the infiltration of M2 TAMs ($CD163^+$) is a significant risk factor for ccRCC patients. Those with a high density of M2 TAMs may have a poorer prognosis. These results emphasize the importance of considering macrophage subtypes in ccRCC prognosis and treatment planning.

List of Abbreviations

TAMs tumor-associated macrophages

ccRCC clear cell renal cell carcinoma

IHC Immunohistochemistry

ROC receiver operating characteristic

AUC area under the curve

RCC Renal cell carcinoma

Scr serum creatinine

GFR glomerular filtration rate

TS tumor stroma

TN tumor nest

OS overall survival

HRs hazard ratios

Clinical Trial Number: 2023-YHD-048

Declarations

Ethics Approval and Consent to Participate: The studies involving human participants were reviewed and approved by the ethics committee of the affiliated Yantai Yuhuangding hospital of Qingdao university. The patients/participants provided their written informed consent to participate in this study.

Consent for Publication: Not applicable.

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article.

Competing Interests: All authors had no conflicts of interest to declare.

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Author Contribution: Conceptualization: Jitao Wu. Data curation: Yingying Yang, Tianqi Wang. Formal analysis: Yingying Yang, Tianqi Wang. Funding acquisition: Jitao Wu. Investigation: Yingying Yang, Xiaohong Ma. Methodology: Yingying Yang, Tianqi Wang, Xiaohong Ma. Project administration: Jitao Wu. Resources: Yingying Yang, Tianqi Wang, Di Sun. Software: Yingying Yang, Tianqi Wang, Di Sun. Supervision: Jitao Wu. Writing original draft: Yingying Yang. Writing review & editing: Jitao Wu.

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