Correlation between CXCR4 and MMP-2 Expression

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RESEARCH ARTICLE

Correlation between CXCR4 and MMP-2 Expression with T Stage in Clear Cell Renal Cell Carcinoma

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ABSTRACT:

Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer with high mortality. Escalation of T stage associates with worse survival. Proper and significant biomarker examination necessary to determine the predictive factor and the opportunity of targeted therapy as well. Upregulated CXCR4 expression on cancer cell promotes its aggressive growth, dissemination, metastasis, and conventional therapy resistance. Overexpression of CXCR4 may induce MMP-2 activity on tumor cell, an enzyme that degrade extracellular matrix and basal membrane particularly, which associated with tumor invasion and metastasis. Those biomarkers activity might be advantaged under hypoxic microenvironment in ccRCC. This study aimed to analyze the role and correlation of CXCR4 and MMP-2 expression with various T stages in ccRCC. Analytic observational study with cross-sectional approach was conducted on 43 formalin-fixed paraffin-embedded tissue of patients diagnosed as ccRCC in Anatomical Pathology Laboratory of Dr. Soetomo Hospital throughout January 2015 until December 2020. CXCR4 and MMP-2 expression were evaluated by immunohistochemistry. Statistical analysis with Kruskal-Wallis and Spearman test were utilized to analyze the expression difference and correlation. Difference of both CXCR4 (p=0.016) and MMP-2 (p=0.029) expression were obtained on various T stages. There was a significant positive correlation between CXCR4 expression (p=0.001) and MMP-2 expression (p=0.002) with T stage, also between CXCR4 with MMP-2 expression in various T stage of ccRCC (p=0.000). In conclusion, this study exhibited that CXCR4 and MMP-2 expression showed synergistic and positive correlation with T stage and might be considered as the basis of targeted therapy in ccRCC.

KEYWORDS: Clear cell renal cell carcinoma, CXCR4, MMP-2, T stage, kidney cancer.

INTRODUCTION:

Renal cell carcinoma is a malignant neoplasm originated from renal epithelial cells and encompasses more than 90% of kidney cancer[1]. This carcinoma comprising more than 10 histology and molecular subtypes, which is clear cell type is the most common type (80%) and has high metastasis propensity to bone, lung, and liver[2,3]. The GLOBOCAN statistic report ranked kidney cancer as the 14th most common cancer worldwide, counted for 431.288 new cases in 2020, and the 9th most common cancer in male[4].

Like most of kidney neoplasms, clear cell renal cell carcinoma (ccRCC) is more common in men rather in women with ratio approximately 2:1[3,5].

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The peak age incidence of this malignancy is within 60-70 years[5,6]. A study in Indonesia showed that the incidence of kidney cancer is 2.4–3 cases in 100.000 population[7].

Morphology characteristic of clear cell renal cell carcinoma is rich in lipid and glycogen content, as well as high vascularity, indicating that altered fatty acid and glucose metabolism is occurred during the development of tumor cells[1,3]. High lipid and glucose content in the cytoplasm of tumor cells will lysis during histopathology process, resulting a clear to mild eosinophilic cytoplasm, thus giving a clear cell appearance[8]. This carcinoma mostly occurred sporadically, only 2-4% cases are hereditary. Inactivation of von Hippel-Lindau (VHL) gene underlying the development of this tumor cells, both in sporadic and hereditary cases[8,9]. Tumor stage is the most important parameter affecting survival in ccRCC,

followed with tumor grade[10,11]. Staging of renal cell carcinoma refers to WHO/8th edition of AJCC (American Joint Committee on Cancer) TNM staging system[12]. T stage is generally based on local extension of primary tumor and invasion into the surrounding adjacent tissue, consists of stages T1 to T4[3,11]. An increase of T stage associated with worse survival, recurrency, and prognosis[11].

Chemokine is a peptide mediator that involved in normal cell development, immune regulation, hematopoietic regulation, wound healing process and inflammation, however overexpression in cancer cells may induce a negative effect. Increased chemokine plays a role in facilitating communication between cancer cells and neoplastic cells in the tumor microenvironment, including endothelial cells, fibroblast, neutrophil activation, and tumor-associated macrophages[13]. The chemokine CXCL12 (Chemokine C-X-C motif ligand 12) binds to its specific receptor, CXCR4 (Chemokine C-X-C motif receptor 4), which through various divergent pathways causes chemotaxis, thereby, increasing intracellular calcium, cell adhesion, cell survival, cell proliferation, and gene transcription[14]. The role of CXCL12/CXCR4 axis is commanded by cancer cells to facilitate the spread of CXCR4-containing tumor cells to highly CXCL12 concentrated tissue. The strong expression of CXCR4 in cancer cells contributes to tumor growth, invasion, angiogenesis, regional lymph node involvement, distant metastasis, relapse, and therapy resistance, leading to poor outcomes, including in ccRCC[15,16].

Loss of VHL protein function in ccRCC will lead hypoxia condition in cells and HIF-1α (Hypoxia-Inducible Factor 1α) accumulation, which will enhance CXCR4 expression[14,17,18]. Overexpression of CXCR4 is an important predictive and prognostic factor for disease progression, aggressiveness, and metastasis in ccRCC, as well as a potential target for anti-cancer therapy[15,16,19]. Overexpression of CXCR4 in cancer cells increase AKT and ERK phosphorylation, also induces the expression and activity of matrix-metalloproteinases (MMPs) such as MMP-2[20,21,22].

One of the subgroups of MMPs is gelatinase, namely matrix metalloproteinase-2 (MMP-2), which plays a role in tumor invasion and metastasis by degrading type IV collagen, which is a major component of the basement membrane and extracellular matrix[23]. The expression and activity of MMP-2 is intensively studied, which often increased in human malignancies and positively correlated with tumor stage, lymph node involvement, increased distant metastasis, and poor prognosis[24]. Increased expression of CXCR4 and MMP-2 in tumor cells under VHL protein inactivation resulting in cell hypoxia may promote more aggressive tumor progression[23,25]. To date, no study has been published regarding the correlation of CXCR4 and MMP-2 expression in clear cell renal cell carcinoma in Indonesia. This study was conducted to analyze the role and correlation of those biomarkers in a referral hospital in East Java, Indonesia.

MATERIALS AND METHODS:

Research Design and Sample:

This analytical observational study was conducted on archived formalin-fixed paraffin-embedded tissue samples obtained from 43 patients who underwent nephrectomy and diagnosed as clear cell renal cell carcinoma in Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, throughout January 2015 until December 2020. The clinical data comprising patient's gender and age obtained from medical record data. Medical records were also reviewed and documented regarding the data of tumor size and tumor extension into renal capsule, perirenal fat, renal sinus, renal pelvis, major renal vein, fascia Gerota, also ipsilateral adrenal gland. The pathological parameters in this study were T stage, CXCR4 expression and MMP-2 expression. All of the H&E-stained slides from each case were reviewed and tumors were histologically classified into 4 groups of T stage according to WHO/AJCC TNM classification for renal carcinoma: T1 (n=6), T2 (n=21), T3 (n=13), and T4 (n=3). Expression of CXCR4 and MMP-2 were evaluated using immunohistochemistry. Ethical approval for this research was issued by Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (Reference number: 0482/LOE/301.4.2/VI/2021).

Immunohistochemical Staining:

Immunohistochemical (IHC) staining was performed on 4-μm-thick, formalin-fixed, paraffin-embedded tissue sections using microtome device (Leica Biosystems), placed on poly-L-Lysine coated glass slide, placed in hotplate (55°C) for 1 hour, left overnight in room temperature. Slides were dewaxed with xylenes 3 times, 5 minutes each, and then rehydrated through a gradual concentration series of alcohol, 2 minutes each. Antigen retrieval was processed with target retrieval solution/sodium citrate buffer in decloaking chamber at temperature 90°C for 45 minutes. Endogenous peroxidase and non-reactive background staining were blocked by 3% H2O2 for 20 minutes at room temperature. Primary antibody with CXCR4 monoclonal antibody (1:100 dilution, CXCR4 [4G10]: sc-53534, Santa Cruz Biotechnology) and MMP-2 monoclonal antibody (1:100 dilution, MMP-2 [8B4]: sc-13595, Santa Cruz Biotechnology) were applied on all samples at 4°C, incubated overnight and then washed in tris-buffered saline. Secondary antibody was applied using biotin-streptavidin-peroxidase kit. A chromogen, 3,3'-

Diaminobenzidine, then applied for 15 minutes on all samples, washed with water, and then counterstained with Mayer's hematoxylin, dehydrated in alcohol gradual concentration series, cleared with xylenes, and finally mounted. Normal lung alveoli tissue was used for positive control of CXCR4 staining. Invasive breast carcinoma tissue was used for positive control of MMP-2 staining.

CXCR4 staining was observed on the cytoplasm, membrane, and nucleus of the tumor cells. MMP-2 staining was observed on the cytoplasm of the tumor cells. Both CXCR4 and MMP2 staining on tissue section was assessed at least on 1000 tumor cells with the highest density cells, using immunoreactive score (IRS) which is a semi-quantitative scoring system that considering the staining intensity and the extent of stained cells, that has been widely accepted and used in previous study[18,26,27,28,29,30,31]. The immunostaining intensity was scored as 0 (no staining), 1(weak), 2 (moderate), and 3(strong). The extent of immunostaining was scored as 0 (0%), 1(1% - 10%), 2 (>10% - 50%), 3(>50% - 80%), and 4(>80%). The final immunoreactive score was determined by multiplying the intensity score with the extent of positive stained cells score. The minimum score is 0 and the maximum score is 12. For statistical purpose, final immunoreactive score was classified into 4 groups. Score equal to or less than 1 was considered as negative, score 2 – 3 was considered as weak positive, score 4 – 5 was considered as moderate positive, and score 6 or more was considered as strong positive. Immunostaining evaluation was carried out using Olympus CX41RF light microscope at 400x magnification by 2 pathologists who were blinded to the patient's data and stage information, and also microscopically recorded using Olympus DP2-BSW. If scoring discrepancies were found between the observers, the slides were reevaluated and final interpretation determined. The concordance rate was more than 95% between the observers.

Statistical Analysis:

SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) was utilized for all statistical analysis. Kruskal-Wallis test was used to analyze the expression difference of CXCR4 and MMP-2 in various T stages. Spearman's correlation test was used to analyze the correlation of CXCR4 expression with various T stages, MMP-2 expression with various T stages, and CXCR4 expression with MMP-2 expression in various T stages. The significance of those statistical analysis results was confirmed when p-value is < 0.05.

RESULTS:

The patients were ranged from age 29 to 69 years old, with the average of patient's age was 53.60±9.63 years, and the highest age group was within 41-50 years group interval, amount for 16(37.2%) patients. Male sex was the majority against female, 30(69.8%) cases and 13 (30.2%) cases, respectively, with a ratio 2.3:1. The highest distribution of T stage was found on stage T2, counted for 21(48.8%) cases, followed by stage T3, T1, and T4. The clinicopathological characteristics of the samples are shown in Table 1.

Table 1. Characteristic of clinicopathological profile

Characteristics		n (%)
Age	21 – 30 years	2 (4.7)
	31 – 40 years	0 (0)
	41 – 50 years	16 (37.2)
	51 – 60 years	12 (27.9)
	61 – 70 years	13 (30.2)
Sex	Male	30 (69.8)
	Female	13 (30.2)
T stage	T1	6 (14)
	T2	21 (48.8)
	T3	13 (30.2)
	T4	3 (7)

CXCR4 expression in clear cell renal cell carcinoma:

CXCR4 expression was found on the cytoplasm, membrane, or nucleus of tumor cells. This study evaluated the overall staining without differentiating the staining location. Tumor with positive strong staining showed a strong staining on the cell cytoplasm rather in membrane or nucleus (Figure 1). CXCR4 evaluation was carried out with immunoreactive score. Only 2 (4.7%) cases exhibited a negative CXCR4 expression, while 25 (58.1%) cases showed a strong positive expression. A significant difference of CXCR4 expression between various T stages was revealed with p-value = 0.016. Spearman correlation test revealed a highly significant positive correlation between CXCR4 expression and various T stages in ccRCC ($r_s = 0.48$, $p = 0.001$). Statistical analysis results are shown on Table 2 and Figure 2.

Table 2. Association between CXCR4 expression and T stage

	CXCR4 expression				p-value [a]	r_s [b]	p-value [b]
	Negative n (%)	**Weak Positive n (%)**	**Moderate Positive n (%)**	**Strong Positive n (%)**			
T Stage					0.016	0.48	0.001
T1	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)			
T2	1 (4.8)	2 (9.5)	7 (33.3)	11 (52.4)			
T3	0 (0)	0 (0)	3 (23.1)	10 (76.9)			
T4	0 (0)	0 (0)	0 (0)	3 (100)			

a: Kruskal Wallis test applied, p-value < 0.05 considered as significant.
b: Spearman correlation test applied, p-value < 0.05 considered as significant.

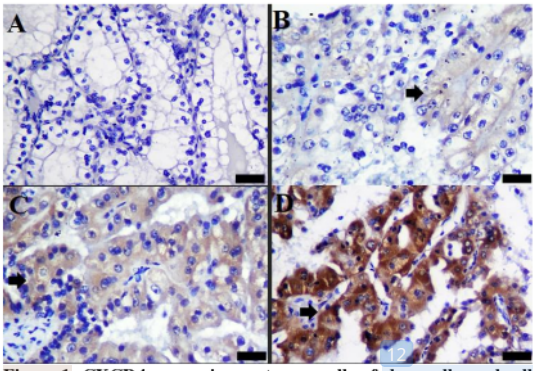
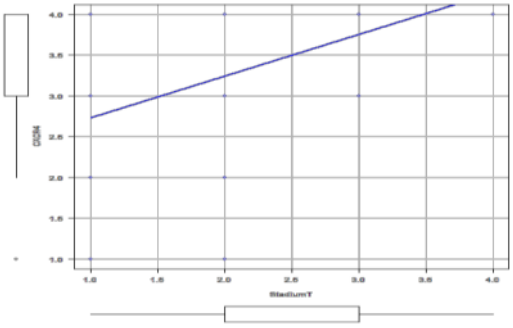


Figure 1: CXCR4 expression on tumor cells of clear cell renal cell carcinoma. The tumor cells were stained on cell cytoplasm, membrane, or nucleus (IHC, 400x magnification). A). Negative expression (IRS score 0 – 1). B). Weak positive expression (black arrow) (IRS score 2 – 3). C). Moderate positive expression (IRS score 4 – 5). D) Strong positive expression (IRS score ≥ 6) with strong cytoplasm staining. Black bar: 50 μm.



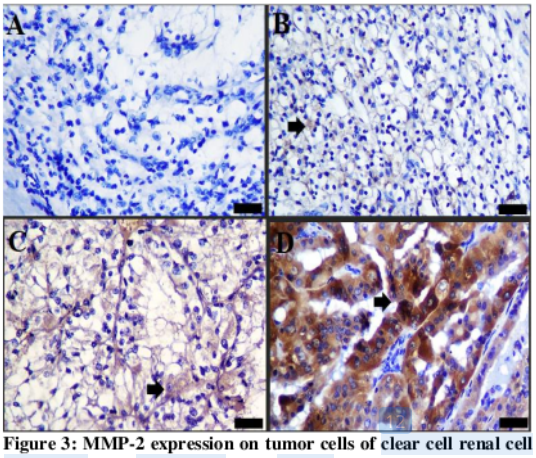


Figure 3: MMP-2 expression on tumor cells of clear cell renal cell carcinoma. The tumor cells were stained on cell cytoplasm (IHC, 400x magnification). A). Negative expression (IRS score 0 – 1). B). Weak positive expression (black arrow) (IRS score 2 – 3). C). Moderate positive expression (IRS score 4 – 5). D) Strong positive expression (IRS score ≥ 6) with strong cytoplasm staining. Black bar: 50 μm.

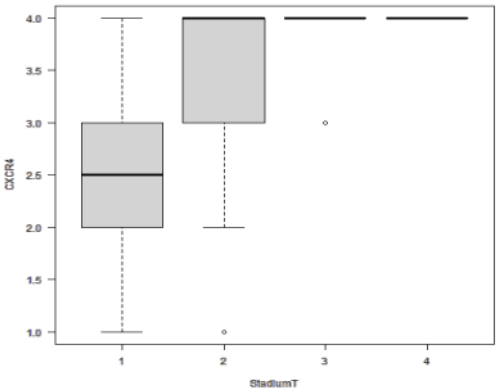


Figure 2. Statistical analysis diagram of CXCR4 and T stage. A). Boxplot diagram of CXCR4 expression difference in various T stages. B) Scattered plot diagram of CXCR4 correlation with T stage in clear cell renal cell carcinoma.

MMP-2 expression in clear cell renal cell carcinoma:

MMP-2 expression was found on the cell cytoplasm (Figure 3). MMP-2 evaluation was carried out with immunoreactive score. Only 2 (4.7%) cases exhibited a negative MMP-2 expression, while 20 (46.5%) cases showed a strong positive expression. A significant difference of MMP-2 expression between various T stages was revealed with p-value = 0.029. Spearman correlation test revealed a highly significant positive correlation between MMP-2 expression and various T stages in ccRCC (r_s = 0.46, p = 0.002). Statistical analysis results are shown on Table 3 and Figure 4.

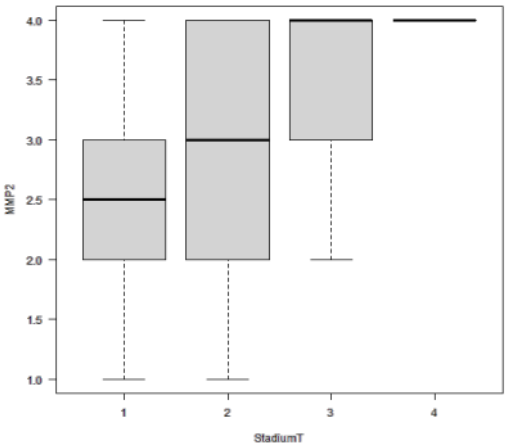


Table 3. Association between MMP-2 expression and T stage

	MMP-2 expression				*p*-value [a]	r_s [b]	*p*-value [b]
	Negative n (%)	Weak Positive n (%)	Moderate Positive n (%)	Strong Positive n (%)			
T Stage					0.029	0.46	0.002
T1	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)			
T2	1 (4.8)	6 (28.6)	7 (33.3)	7 (33.3)			
T3	0 (0)	2 (15.4)	2 (15.4)	9 (69.2)			
T4	0 (0)	0 (0)	0 (0)	3 (100)			

a: Kruskal Wallis test applied, *p*-value < 0.05 considered as significant.
b: Spearman correlation
test applied, *p*-value < 0.05 considered as significant.

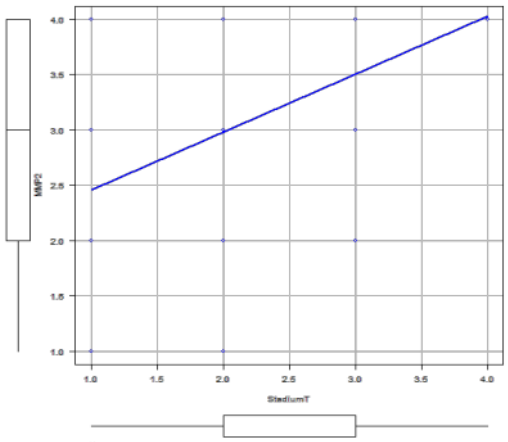


Figure 4: Statistical analysis diagram of MMP-2 and T stage. A). Boxplot diagram of MMP-2 expression difference in various T stages. B) Scattered plot diagram of MMP-2 correlation with T stage in clear cell renal cell carcinoma.

Correlation between CXCR4 and MMP-2 expression in various T stages of clear cell renal cell carcinoma

A highly significant positive correlation was revealed between CXCR4 and MMP-2 expression in various T stages of clear cell renal cell carcinoma (r_s = 0.79, p = 0.000). Statistical analysis results are shown on Table 4.

Table 4. Spearman's correlation test result of association between CXCR4 expression and MMP-2 expression in clear cell renal cell carcinoma

		MMP-2 expression
CXCR4 expression	r_s	0.79
	p	0.000
	n	43

DISCUSSION:

The total number of clear cell renal cell carcinoma cases within 6 years in this study was 43 patients. The average age of patients was 53.6 years, this result was different with previous investigation in America that obtained 64 years as the average patient's age[5], but slightly closer to previous study in Indonesia which found the highest age range of kidney cancer is between 51 – 65 years interval[32]. Most of ccRCC patients in this study was male (69.8%) and ratio male to female was 2.3:1. This finding is consistent with earlier investigations[3,5,32]. The risk factors may be due to smoking habits, excessive alcohol consumption, hypertension, and occupational exposure to trichloroethylene industrial materials which are more common in men[3,5].

Surveillance, Epidemiology, and End Results (SEER) data showed that most kidney cancer patients present with local stage conditions (65%), namely T1-T2 or TNM stage I-II[11]. This study found almost the same result, that the distribution of the most patients was in the T2 group (48.8%) and when combining T1 and T2, 62.8% of cases will be obtained. The classic symptoms of kidney cancer such as hematuria and low back pain at flank region are likely to prompt patients to seek medical attention.

Expression of CXCR4 in this study evaluated on all T stages of ccRCC, that stained on cell cytoplasm, membrane, or nucleus. Evaluation of CXCR4 count the overall staining without differentiate the staining location, however the majority staining located on cell cytoplasm or membrane and only a few samples stained on nucleus. Tumors with strong positive CXCR4 expression appeared to stain strongly on the cytoplasm of the tumor cells, compared to tumors with moderate or weak expression. The result of difference analysis showed that there was a significant difference of CXCR4 expression with various T stages, where as an increase in CXCR4 expression was synergistic with an increase in T stage. Only 4.7% cases exhibited a negative CXCR4 expression, while 95.3% showed positive expression and 58.1% cases showed a strong positive expression.

Previous study by Zagzag et al., was in line to this study which found that the majority of kidney cancer samples showed staining on the cytoplasm, only few samples on the nucleus and membrane[18,33]. On the other hand, a study by An et al., found that CXCR4 staining was predominantly on the nucleus of ccRCC cells and its expression correlate with tumor size[34]. Wang et al., found that renal cell carcinoma A-498 cells showed CXCR4 expression on the cell surface, 30-60 minutes after the cells were stimulated with CXCL12 resulted in rapidly loss cell surface expression, but its expression was completely diffused on cytoplasm and nucleus after

24 hours[35]. CXCR4 expression was found in 65.4% of ccRCC patients, with 36.8% of patients showing strong immunoreactivity and associated with a poor prognosis[19]. The results of this study, however, differ from study by Floranovic et al., who found that the positive expression of CXCR4 in both cytoplasm and tumor cell showed no difference with larger tumor size and tumor grade[34,36].

VHL protein has the capacity to degrade HIF under normal oxygenation conditions[37], resulting in HIF-dependent activation of CXCR4[38]. Another study showed that high expression of CXCR4 was found in the nucleus, cytoplasm, and tumor cell membranes that did not undergo necrosis in ccRCC, both in tumors with hereditary VHL syndrome and sporadically. Vascular cells in these tumors also express CXCR4. This suggests that the VHL-HIF-1 pathway regulates the expression of CXCR4 and its ligands. Hypoxia increases the expression of CXCR4 through the activation of HIF-1 in monocytes, macrophages, endothelium and cancer cells. These findings suggest that involvement of CXCR4 and CXCL12 occurs via autocrine and/or intracrine mechanisms[18,39].

This study exhibited a highly significant correlation between CXCR4 expression and T stage. The CXCR4/CXCL12 axis has a critical role in therapy resistance in various ways, one of them is by directly causing survival, invasion of cancer cells and proliferation of tumor cells, further attracting bone marrow-derived myeloid cells which indirectly facilitate tumor recurrence and metastasis, and cause angiogenesis[40,41,42]. The result of this study is in line with the study by Balshy et al., that found strong positive expression of CXCR4 was associated with an increase in tumor size[43]. Study by An et al., who assessed the correlation of CXCR4 expression with tumor size and tumor necrosis in ccRCC found that there was a positive correlation between CXCR4 expression with primary tumor size and tumor necrosis, supporting that CXCR4 expression could influence tumor growth[34]. Wehler et al., found in their study that CXCR4 expression was correlated with T stage in renal cell carcinoma, where the researchers divided stage T into 2 groups, namely T1-2 and T3-4[33]. Otherwise, a study by D'Alterio et al., found that there was no correlation between CXCR4 expression and T stage in renal cell carcinoma[44].

The role of CXCR4 in tumor growth initiation was confirmed by the role of CXCR4 antagonists that can inhibit tumor growth in several orthotopic experimental and subcutaneous human xenografts[45,46,47,48]. It supports the opportunity for targeted anti-CXCR4 therapy in various malignancies, such as low molecular weight CXCR4 antagonist AMD3100 (Plerixafor) which continues developed in the trial phase on various cancers[42,49,50].

The expression of MMP-2 in this study was observed in the four groups of T stages in ccRCC. Tumors with strong positive expression of MMP-2 were stained strongly on the cell cytoplasm. Only 4.7% cases exhibited a negative CXCR4 expression, while 95.3% showed positive expression and 46.5% cases showed a strong positive expression. All (100%) samples of stage T4 exhibited a strong positive expression whereas among stage T1 and T2 groups still showed a negative expression. A significant MMP-2 expression difference was obtained in various T stages. Some cases in this study showed stronger MMP-2 expression in tumor peripheral area that invaded the adjacent connective tissue stroma, compared to the central area of the tumor. This finding was in line with the literature which states that the integrity of the extracellular matrix surrounding tumor cells affects the behavior of the tumor and if disturbed, it can facilitate local invasion and distant metastatic spread[51]. Study by Kurban et al., found that highly invasive renal cell carcinoma with VHL inactivation showed increased levels and activity of MMP-2[52].

A significant correlation between MMP-2 expression and T stage was found in this study. In contrast with a study on renal cell carcinoma by Kallakury et al., that found no correlation of MMP-2 expression with advanced stages (T3 and T4)[54]. Study by Ahmad et al., using body serum with the ELISA method also showed no correlation between MMP-2 expression and tumor size in renal cell carcinoma[55]. Nonetheless, this study is in line with melanoma research which found that MMP-2 expression was associated with tumor progression both primary and metastatic tumors[53]. Moreover, study in prostate cancer found that MMP-2 was expressed by tumor cells in 70% of cases and by stromal cells around the tumor in 75.9% of cases, which associated with Gleason score, T stage, and decreased disease-free survival[56]. Study in colorectal adenocarcinoma also shown a highly significant correlation between MMP-2 expression and T stage[57].

MMP-2 plays an important role in kidney cancer growth, which predominantly degrades basement membrane components. The extracellular matrix supports tumor cell localization, facilitating communication between tumor cells and their stroma. The interaction between the VHL/HIF protein signaling axis and the activated kinase linkage results in aberrations in the extracellular matrix leading to tumor progression and invasion[51,58]. Regulation of the extracellular matrix in renal cell carcinoma occurs

through both HIF-dependent and HIF-independent pathways. Loss of VHL will result in downregulation of intercellular connective proteins that will contribute to increased motility and tumor cell invasion[52]. A positive correlation between strong MMP-2 expression and T stage in ccRCC can be used as a basis for second-line therapy of ccRCC after conventional therapy, such as chemotherapy or radiation with MMPs inhibitors such as Marastat and BMS-275291, or anti-MMP-2 VHH-29 which is recently being developed[59,60,61].

A highly significant positive correlation between CXCR4 expression and MMP-2 expression was found in this study. This is consistent with the literature which states that increased expression of CXCR4 and MMP-2 in tumor cells in pVHL inactivation condition, can increase the potential for more aggressive tumor progression and metastasis dissemination[25]. Studies in ccRCC by Struckmann et al., with ccRCC 786-O VHL-null strain showed a strong relationship between CXCR4 and MMP-2. CXCR4 expression was found very strong in 786-O VHL-null tumor cells, with CXCR4 distribution mainly on the cell surface. MMP-2 expression was also found abundantly in 786-O cells. MMP-2 expression was found higher than MMP-9 expression in ccRCC tumor cells. Restoration of VHL function in these tumor cells showed a loss of CXCR4/CXCL12 expression as well as MMP-2/MMP-9 expression[23]. The results of previous studies are in line with this first study in Indonesia in analyzing the correlation of CXCR4 and MMP-2 in ccRCC, which statistical test results revealed a highly significant positive correlation between CXCR4 and MMP-2 expression at various T stages of ccRCC. This confirms the theory that VHL protein inactivation that occurred in most ccRCCs may promote a strong positive expression of CXCR4 and MMP-2, which will synergize with the proliferation, survival, growth, and migration of invasive tumor cells that will impact a worse prognosis.

CONCLUSION:

The strong positive expression of CXCR4 and MMP2 are significant biomarkers of T stage in clear cell renal cell carcinoma. This study exhibited that CXCR4 and MMP-2 expression showed synergistic and positive correlation with T stage of clear cell renal cell carcinoma. The correlation of CXCR4 and MMP-2 overexpression with high T stage in clear cell renal cell carcinoma can be considered as the basis of targeted therapy.

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CONFLICT OF INTEREST:

The author declares no conflict of interest.

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