Iraqi Journal of Pharmacy 21(1) (2024) 9-14

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage: https://iphr.mosuljournals.com

Research Article:

Evaluation of the Expression of Immunohistochemical Staining of PDL1 in Renal Cell Cancer

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Article Information

Article history:

Received on: 01 December 2023
Revised on: 02 January 2024
Accepted on: 04 January 2024
Published on: 01 March 2024

Keywords:

Renal cell carcinoma
Programmed cell death ligand,
Immunohistochemistry

Abstract

Background and objectives: To evade anti-tumour responses, tumour cells expressed programmed death ligand 1 (PDL1), which play a role in suppressing the adaptive arm of immune systems. It has been disputed, meanwhile, whether PDL1 expression in Renal cell cancer (RCC) has any predictive value. Anti-PDL1 can decrease tumour size, inhibit immunological checkpoints, and improve overall RCC survival. In our study, our primary objective was to evaluate the statement of PDL1 immunostain in RCC. **Methods:** Fifty samples of primary RCC were used in a prospective and retrospective case series research. From Formalin-fixed and paraffin-embedded (FFPE) blocks, hematoxylin and eosin (H and E) stained glass slides were prepared, and the diagnosis was updated. PDL1 immunohistochemical stain (PDL1 IHC) was conducted for all cases, using the EnVision FLEX visualization system on Autostainer Link 48 with PDL1 IHC 22C3 pharmDx (Dako) monoclonal mouse anti-PDL1. **Results:** PDL1 is found to be expressed in (56 %). The mean age of patients was (54.8±13.52) years, most of them were in their 50s and 60s year old, with male to female ratio of 1.94:1. Clear cell RCC consists of (78%), and most common in stage 1 and stage 3 with statistically significant p–value. Clear cell carcinoma was statistically significant with stage 1 and 3 and grade 2 was the most frequent. The majority of instances of clear cell RCC were on the left side. **Conclusion:** PDL1 provide an excellent template for confirming the diagnosis of RCC.

1. Introduction

Renal cell carcinoma (RCC) makes up 1-3% of all human cancers and 75–80% of adult renal cancers (1). RCC is the 12th most prevalent malignant neoplasm overall, excluding blood cancers (2). Geographically, incidence varies greatly, with North America and Europe often having greater rates (3). Older persons are more susceptible to sporadic RCC. Although most individuals are diagnosed between the ages of 65 and 74, the average age of diagnosis in the US is 64 (4). The World Health Organization's (WHO) categorization of urogenital tumours combines immunohistochemistry and pertinent molecular testing with morphologic diagnostic criteria. Massively parallel sequencing will be used globally, which will cause a change in diagnostics from morphological to molecular analysis (5). Programmed death ligand 1 (PDL1; also known as CD274 and B7-H1) is a 33-kDa type 1 transmembrane glycoprotein that is part of the B7 class. It is composed of 290 amino acids and has immunoglobulin (Ig) structure and IgC domains in its extracellular region (6). PDL1 is often expressed by macrophages, certain T and B cells that have been activated, dendritic cells, and some epithelial cells, especially when there is inflammation (7). Furthermore, tumour cells expressed PDL1 as an "adaptive immune mechanism" to evade anti-tumour reactions (8). It has been disputed, meanwhile, whether PDL1 expression in RCC has any predictive value (9). In the meanwhile, normal human cells do not express PDL1, but neoplastic cells and antigen-presenting cells do. Recent results showed that invasive findings and a poor prognosis are associated with the expression of PDL1 in RCC (10). Immune checkpoint inhibition is a commonly used systemic immune treatment for RCCs that are not candidates for surgery or distant metastases (11). Anti-PDL1 can decrease tumour size, inhibit immunological checkpoints, and improve overall RCC

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How to cite:

Al-Nuaimy , R., ME., Al-Azzo , N., SM., (2024). Evaluation of the Expression of Immunohistochemical Staining of PDL1 in Renal Cell Cancer. Iraqi J. Pharm. 21(1), 9-14.

DOI: **https://doi.org/10.33899/iphr.2024.145039.1071**

survival (12). The present study aimed to assess the expression of PDL1 immunostain in RCC sample of human.

2. Materials and methods

2.1. Study design

A case series research, both prospective and retrospective, was conducted on fifty primary renal cell cancer samples, which were collected from some teaching hospitals and private laboratories in Mosul City over 7 months extending from November 2022 to May 2023. Biopsy types are collected from patients undergoing operation of either radical or partial nephrectomy, then tissue sectioning done for histology and immunohistochemistry step.

2.2. Histology and immunohistochemistry

Formalin-fixed and paraffin-embedded (FFPE) blocks were used to prepare hematoxylin and eosin (H and E) stained glass slides. The slides were then reviewed for diagnosis and other histopathological criteria, such as histological type, grade, and pathological stage. The medical information includes age, sex, and laterality from patient medical records (13,14).

PDL1 immunohistochemical stain (PDL1 IHC) was conducted for all cases on FFPE tissues of the tumour, PDL1 IHC 22C3 pharmDx (Dako) monoclonal mouse anti-PDL1, clone 22C3 is expected to be used with the EnVision FLEX visualization system on Autostainer Link 48 to identify the PDL1 protein in Formalin-fixed and paraffin-embedded (FFPE) blocks (15).

By utilizing the appropriate reagent, keeping track of the incubation period, cleaning slides in between reagent applications, and preventing nonspecific background staining with hematoxylin counterstain by incubating for five minutes, the automated method completed the staining and counterstaining procedures. Since it is a more affordable alternative, an external positive control (a tonsil) is used in the testing. Additionally, the negative sections of the positive control tissue used as the negative control tissue (16).

Based on the degree and percentage of tumour cells exhibiting either cytoplasmic or membrane staining, PDL1 expression was assessed and assigned a 0, negative (no immunoreactivity), score 1, weak (5% to less than 25% of cells), 2, moderate (between 25 and 60% of cells), and 3, strong (more than 60% of cells) are the four immunoreactive states (17).

Regardless of staining strength or whether the membrane exhibits entire or partial PDL1 positivity, a viable tumour cell expressing PDL1 possesses membranous staining. If a tumour cell exhibits cytoplasmic staining but not membrane staining, it is said to be PDL1-negative.

At lower magnifications (100x) the tumour areas in the slide were evaluated for adequacy of functional tumour cells so evaluation of PDL1 staining and non-staining tumour cells to confirm that there are at least 100 viable tumour cells in the sample. At higher magnification (400x), examination of PDL1 expression in the tumour and by dividing the slide into multiple areas, each area is evaluated.

2.3. Statistical analysis

This descriptive analysis of the collected data was analyzed using the IBM- Statistical Package for Society Study (SPSS, USA) for Windows version 25. The frequency and corresponding percentage of the data were evaluated by the use of the Chi-square test. With a 95% confidence interval, a p-value of 0.05 or less was deemed statistically significant.

3. Results

The patient's ages were between 21 and 77 years, with a mean age of (54.8±13.52) years, They were mostly in their fifth and sixth decades (**Figure 1**).

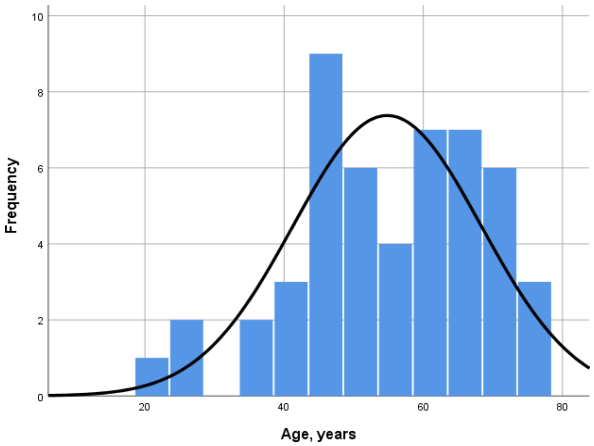

Figure 1. Age distribution among RCC cases.

The studied sample consists of 33 (66%) males and 17 (34%) females with male to female ratio of 1.94:1 (**figure 2**).

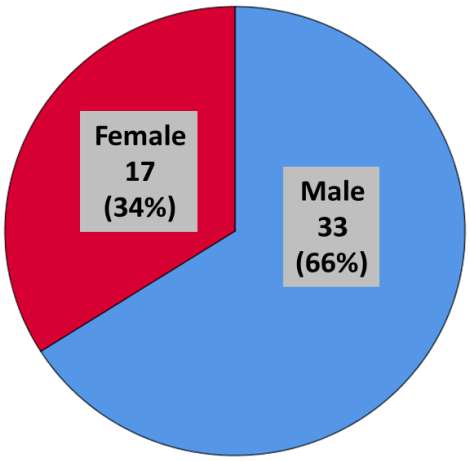

Figure 2. Gender distribution among RCC cases.

In this study, histological types were clear cell RCC consisting of 39 (78%), papillary RCC 8 (16%), and chromophobe RCC 3 (6%) (**Figure 3**).

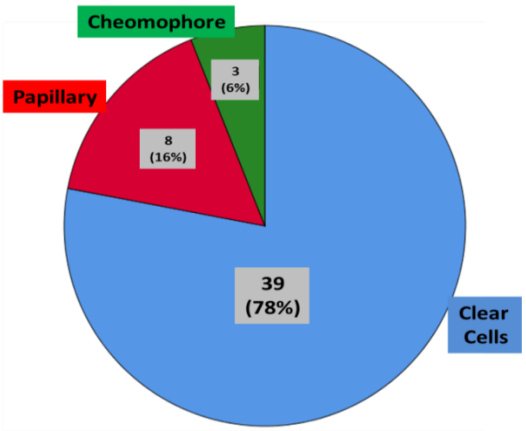

Figure 3. Frequency of histological types of RCC cases.

Regarding the stages of cancer, in 43 cases from our sample (only 7 cases their stages were not reported), stage 1 and stage 3 were most common in clear cell RCC; 16/32 (50%) and 13/32 (40.6%) respectively, with statistically significant (p=0.0001) differences. Papillary RCC was statistically non-significant (p=0.6) and most common in stage 1 in 4/8 (50%) cases, the chromophobe was also most common in stage 1 with 2/3 (66.7%) statistically non-significant (p=0.5) (**Table 1**).

Table 1. Frequency of stages among different histological variants in RCC

Stage	Histopathology variant			*p-value**
	Clear cell (n=32)	Papillary (n=8)	Chromophobe (n=3)	
1	16 (50%)	4 (50%)	2 (66.7%)	***0.7***
2	2 (6.3%)	2 (25%)	-	
3	13 (40.6%)	2 (25%)	1 (33.3%)	
4	1 (3.1%)	-	-	
p-value**	0.0001	0.6	0.5	

Out of 50 cases (only 3 cases their grade were not reported), grade 2 was most frequent in clear cell RCC 18/36 (50%), 3 /36(8.3%) in grade1, 9 /36 (25%) in grade 3, also clear cell RCC was 6/36 (16.7%) in grade 4 with statistically significant (p=0.003) difference while papillary RCC statistically non-significant with grade (p=0.1) (**Table 2**).

Table 2. Frequency of grade in different histological variants of RCC

Grade	Histopathology variant			p value *
	Clear cell (n=36)	Papillary (n=8)	Chromophobe (n=3)	
1	3 (8.3%)	-	-	*0.1*
2	18 (50.0%)	6 (75.0%)	-	
3	9 (25.0%)	2 (25.0%)	3 (100.0%)	
4	6 (16.7%)	-	-	
p-value**	0.003	0.1	-	

The tumour laterality of 50 cases (only 3 cases their laterality were not reported), the majority of RCC with clear cell cases 23/36 (63.9%) were on the left side, while 13/36 (36.1%) cases of clear cell RCC were on the right side with statistically significant (p=0.09) differences (Table 3).

Table 3. Laterality according to histological variant in RCC

Laterality	Histopathology variation			p value *
	Clear cell N=36	Papillary N=8	Chromophobe N=3	
Left	23 (63.9%)	4 (50.0%)	2 (66.7%)	*0.7*
Right	13 (36.1%)	4 (50.0%)	1 (33.3%)	
p-value**	0.09	1.0	0.5	

PDL1 is found to be expressed in 28/50 (56 %), and negative expression in 22/50 (44%) with statistically significant (p=0.0001) difference (Table 4)

Table 4. Frequency of PDL1 expression of different PDL1 score

PDL expression	PDL1 score				p value
	0 (n=22)	1 (n=9)	2 (n=8)	3 (n=11)	
-Ve	22	-	-	-	**0.0001**
+Ve	-	9	8	11	
p-value	-	-	-	-	

4. Discussion

As a result of the rise in the prevalence of RCC, numerous research projects have started in the recent few decades (18). Many markers that have a role in the prognosis of RCC have been studied to find out the main target therapy and improve overall survival. The new markers PD-1 and PDL1 are associated with poor prognosis so the use of immunotherapeutic targets such as immune checkpoint inhibitors has a prognostic promise and enhances overall survival, especially in metastatic RCC (19-21).

The average patient age in this research was (54.8±13.52) years. Research on RCC patients whose surgical samples were examined at Sulaymani City (Iraq), with a mean age of 51 years, was the most frequent group (22). Similar, results were reported by previous studies (23,24).

A study conducted by Tabriz *et al.*(2022), among 86 patients revealed older age with an average age of 59 years (range: 40-78 years) (25). On the contrary, a study conducted by Walter *et al.*(2020), reported a younger median age of 48 years at diagnosis ranging from 11 to 81 years old (26).

According to the results of ethnic variation in the histological subtypes of RCC in Singapore, compared to the Malays (55.1 years), the average age (years) at presentation for the Chinese (58.2) and Indians (57.6) was slightly higher (27). This pattern may be caused by differences in the populations of the various ethnic groups covered in the studies under consideration; whilst the Malays made up a sizable fraction of the population in the earlier research, the Chinese made up the greatest percentage in the latter (27).

The male predominance was obvious among the patients of the current study; the male-to-female ratio was 1.94:1. Similar research at Mosul and Tikrit (Iraq) showed that the highest distribution among males to females in a case (28,29), which ran in parallel to the findings in the SEER data in which the frequency of RCC was positively biased towards men in the sex distribution, with a male-to-female ratio of 1.8:1 (30), also the European association of urology

guidelines on RCC stated that 3:2 ratio of male to female (31).

Mohamed *et al.*(2022), research conducted in Somalia found that the kidney mass ratio was 2:1 male to female, indicating a greater than twofold preponderance of men (32). A different outcome was reported by the pooled analysis of data from sub-Saharan African countries; there was a female predominance of RCC compared to males (33,34). Also, the previous study conducted in West Africa revealed female preponderance (35). Because of the increased incidence of RCC in females relative to males, some writers have proposed that estrogens may have a role in the aetiology of the disease. The fact that women frequently get abdominal ultrasound scans for pregnancy may also contribute to the increased likelihood of any solid renal mass being discovered during the ultrasound examination process (34).

RCC must be classified histologically since the many subtypes have a substantial impact on the prognosis and management of these malignancies. In the present study, the most frequent histological type was clear cell RCC followed by papillary RCC and chromophobe RCC. This observation was in line with a study conducted in Mosul /Iraq and Sulaymani City (Iraq), in which the major histologic type was clear cell RCC, followed by papillary RCC and chromophobe RCC (22,28).

In a study in Saudi Arabia, the most common histological subtype was clear cell (conventional) RCC which was higher than papillary RCC and chromophobe RCC (36). In addition, a study conducted in Somalia reported that the clear cell RCC represents the majority of RCC cases and is the most common and aggressive type (32). A review of another previous study found that the most common subtypes of RCC are Clear cell RCC, followed by papillary RCC, and to a lesser extent chromophobe RCC (37,38).

Among the current studied samples, stage I was the most frequently found among the three different studied histological variants moreover, the difference of each variant concerning the stage was significant only in clear cell type. Similarly, The data were obtained in a study conducted in Mosul City (Iraq), and it was found that the most common cases were in stage I (28). In the Saudi Arabia cohort study recorded tumors were detected early such as stage I (39). RCC stage movement over time is demonstrated by available data. According to one theory, more cancers are being discovered in their early stages as a result of the increased usage of cross-sectional scans (39). A similar study in the United States and India found clinical stage I illness was diagnosed more frequently (23,40). This result in Somalia was in contrast to most of the previous studies; the most common cases were in stage II (30), which might be due to late diagnosis.

In the present study, grade II was more frequent in clear cell RCC than other grades with a statistically significant difference, while papillary RCC is statistically not significant with grades. In a similar study in Sulaymani (Iraq), these grade II tumours made up more than half (50.9%) of the classification (22). Mahasin *et al.*(2018), a cohort study conducted in Saudi Arabia, tumours were detected early such as Fuhrman Grade 1 or 2 (39). When comparing the WHO/ISUP grading system to the Fuhrman grading system, Dagher et al. (2017), found that among the 374 instances in the subgroup for which outcome data were available, grade 2 was most common (41). The most frequent histological grade found in Kumar et al. (2019), was grade 3 (23). Mohamed et al.(2022), and according to the WHO/ISUP grading system, 50% of the patients had low-grade tumours, and the other 50% had high-grade tumours (32).

The majority of clear cell and chromophobe RCC instances in the current study were found to be on the left side, however, there was no difference between the left and right sides in terms of papillary type. Although Ali et al.(2023), conducted their study in Sulaymani (Iraq), found 50.4% of the tumours were right-sided(22). These findings revealed a much greater prevalence of renal sinus invasion in right-sided tumours (22). however, Guo et al. (2019), reported a similar rate of 50.6% and noted that right-sided tumours were more likely to exhibit positive pathologic characteristics, including enhanced cancer-specific survival (42). To find persistent changes in tumour features and behavior concerning sidedness and to determine an anatomical foundation for them, more research is necessary (22). Similar results in India found the right kidney was most common according to laterality (43). However, the study by Devendar et al. (2009), showed that the RCC patients' laterality had no impact on their survival (44). Clear cell carcinoma was the most common histological subtype and the tumour's lateralities, which were absent (31.5%), left kidney (31.5%), and right kidney (37.5%), were almost equal (45).

In the present study, PDL1 is found to be expressed in 28 /50 (56 %), according to the previous study in Brazil and Egypt in which, PDL1 expression was similar results to the present study (24,46). Studies conducted in Iran and Germany reported lower results in PDL1 expression compared to this study (25,47). PDL1 expression reported in studies conducted in India and different regions of the USA have shown discrepant PDL1 expression (23,48-50). This discrepancy in the results of PDL1 expression in the mentioned studies is due to different sample sizes and the use of antibodies sources.

5. Conclusion

The researchers found that 56% of the study sample exhibited positive expression of PDL1, a protein associated with immune system regulation. This mean that in 56% of our patients we have a PDL1 protein which can be targeted by anti-PDL1 to imparts a therapeutic advantages.

6. Conflict of interest:

The author declares no conflict of interest in the publication of this study.

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تقييم التعبير عن التلوين الكيميائي المناعي لرباط الموت المبرمج في سرطان خلايا الكلية

الخلاصة

المقدمة والاهداف: للتهرب من الاستجابات المضادة للورم، تقوم الخلايا السرطانية بالإبانة عن رباط الموت الخلوي المبرمج كآلية مناعية متكيفة. وفي الوقت نفسه هنالك خلاف فيما اذا كان زيادة الابانة عن رباط الموت الخلوي المبرمج دليل على حجم الورم او له اي قيمه تنبؤية. علاوة على ذلك فان مضادات الرباط المذكور انفا لها دور في تقليل حجم السرطان الكلوي، تضليل نقاط التفتيش المناعية، وتحسين صحة المريض المصاب بسرطان الكلية بشكل عام. **طرق العمل:** تم تجميع انسجة مرضى السرطان الكلوي بعد عملية استئصال كلي او جزئي للكلية، وبعد تحضير شرائح مجهرية من الكلية، تم تعريض هذه الشرائح للصبغة الاساسية وصبغة المضاد للبروتين المسمى برباط الموت الخلوي المبرمج وتم قياس نشاط هذه البروتينات وبالتالي كميتها (والتي تعبر عن حالة الورم) بتقنية التلوين الكيميائي المناعي. **النتائج:** اظهرت النتائج ان معظم المرضى هم في العقدين الخامس والسادس من العمر وبنسبة اعلى لدى الذكور بالمقارنة مع الاناث. وبينت الشرائح ان الانسجة عبرت عن الابانة عن رباط الموت الخلوي المبرمج بنسبة 56%. واكدت النتائج ان معظم نوع الخلايا هي من نوع سرطان الكلى ذو الخلايا الصافية وان غالبيتها في مرحلتها الثانية وفي الكلية اليسرى اكثر من الكلية اليمنى. **الاستنتاج:** ان رباط الموت الخلوي المبرمج ظهر جليا في الشرائح المختبرية وهذا يؤكد اهميتها في التشخيص.

الكلمات المفتاحية: سرطان خلايا الكلية، رباط الموت الخلوي المبرمج، التلوين الكيميائي المناعي.