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Immunohistochemical Expression of P53 in Renal Cell Carcinoma Subtypes

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Abstract. Kidney cancer is common, accounting for approximately 2.2% of all cancer incidences. Mutation in P53 gene is common among many malignant tumours. More than half of human tumours contain a mutation in the p53 gene. It is reported that p53 immunexpression predicts un-favourable prognosis in various types of cancers. P53 mutation in renal cell carcinoma is uncommon. Findings on the association of p53 expression with renal cell carcinoma prognostic markers such as nuclear grade, histopathological subtypes, lymphovascular invasion and stage are controversy in various studies in the world. This study aims to evaluate the frequency of immunohistochemical expression of P53 in different subtypes of renal cell carcinoma and to assess the association of its expression with some clinicopathological parameters including age, sex, laterality, histopathological subtypes, grade, lymphovascular invasion and tumor stage. In this prospective and retrospective case series study, sixty five cases of surgically excised renal cell carcinoma biopsies were included. The blocks of the cases were collected from Al-Jumhori teaching hospital and some private laboratories in Mosul city (Iraq), in a period from June 2021 to August 2024. Section slides from the appropriate blocks were stained by P53 (immunostain). Interpretation of the slides and statistical analysis have been done. P53 expression was observed in (6.2%) of cases, with male predominance (75%), and in age 55 years and older (75%), mainly involving the right side (75%) and of clear cell subtype (100%), while the papillary and chromophobe cases were negative for P53. Cases with grade III, IV, and (pT) stage T1-T2 showed the most P53 positivity (75%) for each. Regarding lymphovascular invasion (50%) of cases showed positivity for P53. P53 immunexpression was detected in only 6.2% of all studied cases. No significant statistical association was noticed between P53 expression and the studied clinicopathological parameters.

Highlights:

1. P53 expression was found in only 6.2% of RCC cases and all of them were of the clear cell RCC subtype.
2. There was no statistically significant association between P53 expression and clinicopathologic parameters such as age, gender, grade, and stage.
3. P53 expression tended to be more prevalent in male patients aged ≥55 years, high grade (3-4), and right kidney location.

Keywords: P53, Renal Cell Carcinoma, Immunohistochemistry, Clear Cell RCC, Clinicopathological Correlation

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Introduction

Renal cancer represents a significant clinical challenge in contemporary oncology, emerging as a common malignancy affecting the kidneys with substantial implications for patient outcomes. This disease accounts for approximately 2.2% of all cancer incidences worldwide, a statistic that underscores its meaningful contribution to the global cancer burden [1]. The epidemiological trajectory of renal cancer reveals a concerning trend, as its occurrence continues to demonstrate an upward trajectory, reflecting both improved diagnostic capabilities and potentially increasing risk factors in the population.

Within the spectrum of kidney malignancies, renal cell carcinoma (RCC) stands as the predominant pathological entity, representing the primary form of kidney cancer and constituting over 90% of all kidney cancers encountered in clinical practice [1]. This overwhelming prevalence establishes RCC as the focal point for research efforts and therapeutic interventions in renal oncology. The heterogeneous nature of RCC encompasses various histological subtypes, each with distinct biological behaviors and clinical implications.

Among these subtypes, clear-cell renal cell carcinoma (ccRCC) emerges as the most clinically significant variant on a global scale. This particular subtype represents the most prevalent form of kidney cancer worldwide, with approximately 75% of patients diagnosed with RCC ultimately receiving a ccRCC classification [2]. The dominance of ccRCC in the renal cancer landscape reflects both its inherent biological characteristics and its tendency to present in clinical settings, making it the most extensively studied and therapeutically targeted form of the disease.

The clinical presentation and progression patterns of RCC reveal particularly sobering statistics regarding metastatic disease. At the time of initial diagnosis, approximately 30% of RCC patients already harbor distant metastases, indicating advanced disease that significantly complicates treatment approaches and diminishes prognostic outcomes [3]. Even more concerning is the behavior observed in patients who initially present with apparently localized disease. Among those patients with localized RCC who undergo surgical intervention, approximately 40% subsequently develop distant metastases following their surgical treatment [3]. This pattern of disease progression highlights the aggressive nature of RCC and underscores the critical need for effective systemic therapies and improved prognostic markers.

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The molecular landscape of human cancers reveals the central importance of tumor suppressor genes, particularly the p53 gene, in cancer development and progression. The p53 gene holds the distinction of being mutated in more than half of all human tumors, establishing it as one of the most frequently altered genes in cancer biology [4]. This widespread involvement of p53 mutations across diverse cancer types has generated extensive research interest in understanding its prognostic implications across various malignancies.

Clinical investigations have demonstrated that p53 expression serves as a valuable prognostic indicator across multiple cancer types, with documented predictive value in several major malignancies. The prognostic significance of p53 expression has been established in breast cancer, where it correlates with treatment response and patient outcomes. Similarly, gastric cancer patients demonstrate prognostic associations with p53 expression patterns, as do patients with multiple myeloma, colorectal cancer, cervical cancer, and oral cancer [4]. This broad spectrum of prognostic utility across diverse cancer types has established p53 as a potential universal prognostic marker in oncology.

However, when examining the specific context of renal cell carcinoma, the prognostic role of p53 expression presents a more complex and controversial picture. Research findings investigating the association between p53 expression and various RCC prognostic markers have yielded conflicting results, creating ongoing debate within the urological oncology community. Studies examining the relationship between p53 expression and nuclear grade, which represents a fundamental histopathological prognostic indicator, have produced inconsistent findings [5-8]. Similarly, investigations into the association between p53 expression and different histopathological subtypes of RCC have failed to reach consensus.

The controversy extends to other critical prognostic parameters in RCC, including lymphovascular invasion (LVI), which represents an important indicator of aggressive disease behavior and metastatic potential. Studies examining the correlation between p53 expression and LVI have produced variable results, failing to establish a clear predictive relationship [5-8]. Furthermore, investigations into the association between p53 expression and tumor stage, perhaps the most fundamental prognostic indicator in RCC, have similarly yielded contradictory findings across different research groups and patient populations.

This ongoing controversy regarding p53 expression and its prognostic significance

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in RCC reflects the complex molecular biology of this disease and highlights the need for continued research to clarify these relationships. The inconsistent findings may stem from methodological variations between studies, differences in patient populations, variations in p53 detection techniques, or the inherent biological heterogeneity of RCC itself. Understanding these relationships remains crucial for developing more effective prognostic tools and treatment strategies for patients with renal cell carcinoma.

Method

Study design: In this prospective and retrospective case series study, sixty-five cases of surgically excised RCC biopsies were included. The blocks of the cases were from June 2021 till March 2024 and the period of study was conducted from 1st of January 2024 till the 1st of August 2024.Sections from paraffin embedded tissue were taken on clean slides and stained with H and E. The most appropriate block of each case was chosen for immune-histochemical (IHC) staining with P53.This study was performed by using the primary antibody which is P53, isotype IgG1, clone DO-7, Monoclonal mouse anti-human antibody, supplied by Agilent company (USA). The staining done by Autostainer Link 48, using Agilent (Dako) kit, both supplied by Agilent company (USA).

Interpretation of immunohistochemistry staining: Nuclear immunoreactivity for P53 was evaluated and scored manually. The slides were scanned in an average of 10 microscopic fields (400x magnification).The brown pigmentation of the nuclei was detected in tumor cells and if the percentage of nuclear staining of P53 was equal to 10% or more the case was considered positive if less the case was considered negative [5]. Pictures were taken by Leica microscope camera.

Statistical analysis: Statistical analysis was done by using of Chi-square and Fisher exact test when indicated using SPSS software version 26.0 for statistical analysis. A "P value of ≤ 0.05" was considered statistically significant with confidence interval of 95%.

Results and Discussion

A. Results

The analysis of 65 renal cell carcinoma cases reveals distinct demographic patterns that provide insight into the disease's clinical presentation (Table 1). The age distribution demonstrates a notable predominance of older patients, with 38 cases (58.5%) occurring in patients aged 55 years and above, while 27 cases (41.5%) were

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diagnosed in patients under 55 years of age. This age distribution aligns with the established understanding that renal cell carcinoma predominantly affects older adults, reflecting the cumulative nature of genetic alterations and environmental exposures that contribute to carcinogenesis over time.

Gender distribution within this cohort shows a marked male predominance, with 42 cases (64.6%) occurring in male patients compared to 23 cases (35.4%) in female patients. This approximate 2:1 male-to-female ratio is consistent with epidemiological data demonstrating that men are at higher risk for developing renal cell carcinoma, potentially due to occupational exposures, smoking patterns, and other lifestyle factors that historically have shown gender-based differences.

Regarding anatomical distribution, the analysis reveals an interesting laterality pattern with left-sided tumors showing a slight predominance. Left kidney involvement was observed in 39 cases (60.0%), while right kidney tumors accounted for 26 cases (40.0%). This left-sided predominance, while not dramatically skewed, suggests potential anatomical or developmental factors that may influence tumor development, though the clinical significance of this observation requires further investigation.

The histopathological classification of the cases demonstrates the expected predominance of clear cell renal cell carcinoma, which represented 53 cases (81.5%) of the total cohort. This proportion closely mirrors global epidemiological data indicating that clear cell RCC constitutes the vast majority of renal cell carcinomas worldwide. The dominance of this subtype reflects both its inherent biological characteristics and its tendency to present clinically, making it the most frequently encountered variant in surgical series.

Papillary renal cell carcinoma emerged as the second most common subtype, accounting for 9 cases (13.8%) within the study population. This proportion is consistent with established literature indicating that papillary RCC represents the second most frequent histological variant of renal cell carcinoma. The remaining cases consisted of chromophobe renal cell carcinoma, which was observed in 3 cases (4.6%), representing the least common subtype within this cohort. This distribution pattern reflects the typical hierarchical frequency of RCC subtypes encountered in clinical practice and surgical pathology.

The tumor grading analysis reveals a distribution that emphasizes the spectrum of biological aggressiveness within renal cell carcinoma. Grade 2 tumors

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represented the largest single category with 32 cases (49.2%), indicating that nearly half of the cases demonstrated moderately differentiated characteristics. This finding suggests that a significant proportion of patients present with tumors of intermediate biological potential, which has important implications for treatment planning and prognostic counseling.

Higher-grade tumors collectively represented a substantial portion of the cohort, with Grade 3 tumors accounting for 16 cases (24.6%) and Grade 4 tumors representing 11 cases (16.9%). The combined presence of high-grade tumors (Grades 3 and 4) in 41.5% of cases underscores the aggressive nature of a significant subset of renal cell carcinomas and highlights the importance of grade as a prognostic indicator. In contrast, well-differentiated Grade 1 tumors were relatively uncommon, representing only 6 cases (9.2%), suggesting that most renal cell carcinomas that come to clinical attention have progressed beyond the most indolent forms of the disease.

The pathological T-stage distribution provides critical insights into the extent of local disease at the time of surgical intervention. Early-stage disease was well-represented, with T1a tumors accounting for 20 cases (30.8%) and T1b tumors representing 14 cases (21.5%). The combined T1 category, representing organ-confined disease, constituted 52.3% of the cohort, indicating that a substantial proportion of patients presented with localized disease amenable to surgical cure.

T2 disease, representing larger organ-confined tumors, was less common with T2a tumors accounting for 5 cases (7.7%) and T2b tumors representing only 1 case (1.5%). The relatively low frequency of T2 tumors may reflect the tendency for larger tumors to progress to more advanced stages or the effectiveness of modern imaging in detecting tumors before they reach substantial size while remaining organ-confined.

Advanced local disease was represented by T3 and T4 categories, with T3a tumors accounting for 20 cases (30.8%), representing a significant proportion of patients with locally advanced disease involving perinephric fat or renal vein invasion. T3b disease was uncommon with only 1 case (1.5%), while T4 tumors, representing the most locally advanced disease, accounted for 4 cases (6.2%). The substantial representation of T3a disease highlights the importance of careful surgical planning and the potential need for adjuvant therapies in a significant subset of patients.

The evaluation of lymphovascular invasion reveals that the majority of cases,

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specifically 50 cases (76.9%), demonstrated no evidence of lymphovascular invasion, suggesting that most tumors had not yet acquired the ability to invade lymphatic or vascular structures at the time of surgical resection. This finding is generally associated with more favorable prognosis and lower risk of systemic dissemination.

However, lymphovascular invasion was present in 15 cases (23.1%), representing nearly a quarter of the cohort. The presence of lymphovascular invasion in this substantial minority of cases is clinically significant, as it represents an important adverse prognostic factor associated with increased risk of metastatic disease and poorer overall survival. This finding emphasizes the importance of careful histopathological examination for lymphovascular invasion and its incorporation into risk stratification and treatment planning decisions.

The overall distribution of pathological parameters within this cohort reflects the typical spectrum of renal cell carcinoma presentations encountered in clinical practice, with a predominance of clear cell histology, intermediate-grade tumors, and a mix of early and locally advanced disease stages. These findings provide a representative snapshot of the disease's pathological characteristics and underscore the heterogeneous nature of renal cell carcinoma as a clinical entity.

Table 1. The distribution of renal cell carcinoma cases according to the pathological parameters

Variables		No. [total = 65]	Percent %
Age	< 55 years	27	41.5%
	≥ 55 years	38	58.5%
Sex	Male	42	64.6%
	Female	23	35.4%
Site (laterality)	Left	39	60.0%
	Right	26	40.0%
Histopathological subtype	Clear cell RCC	53	81.5%
	Papillary RCC	9	13.8%
	Chromophobe RCC	3	4.6%
Tumor grade (G)	1	6	9.2%
	2	32	49.2%
	3	16	24.6%
	4	11	16.9%
pT stage			
	T1a	20	30.8%
	T1b	14	21.5%
	T2a	5	7.7%
	T2b	1	1.5%
	T3a	20	30.8%
	T3b	1	1.5%
	T4	4	6.2%
Lymphvascular invasion	No invasion	50	76.9%
	Present	15	23.1%

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P53 expression was positive in four cases only (6.2%), while 61 cases (93.8%) were negative. P53 was found to be positive in three cases (75%) who were 55 years and older, and in only one case (25%) who was under 55 years old, with P value was (0.635). In regards to sex, male cases had a higher expression 3 cases (75%) than female cases 1(25%) with P value was (0.654) . For tumors in the left kidney, 38 cases (62.2%) had No P53 expression, while only one case (25%) was positive. In the right kidney, 23 cases (37.7%) had No P53 expression, while three cases (75%) exhibited positivity with P value was (0.140) . In regards to histopathological subtypes all P53 positive cases were of ccRCC subtype four cases (100%) (Figure 1), both papillary (9 cases) and chromophobe (3cases) RCC subtypes had no P53 expression (Figure 2 and 3).

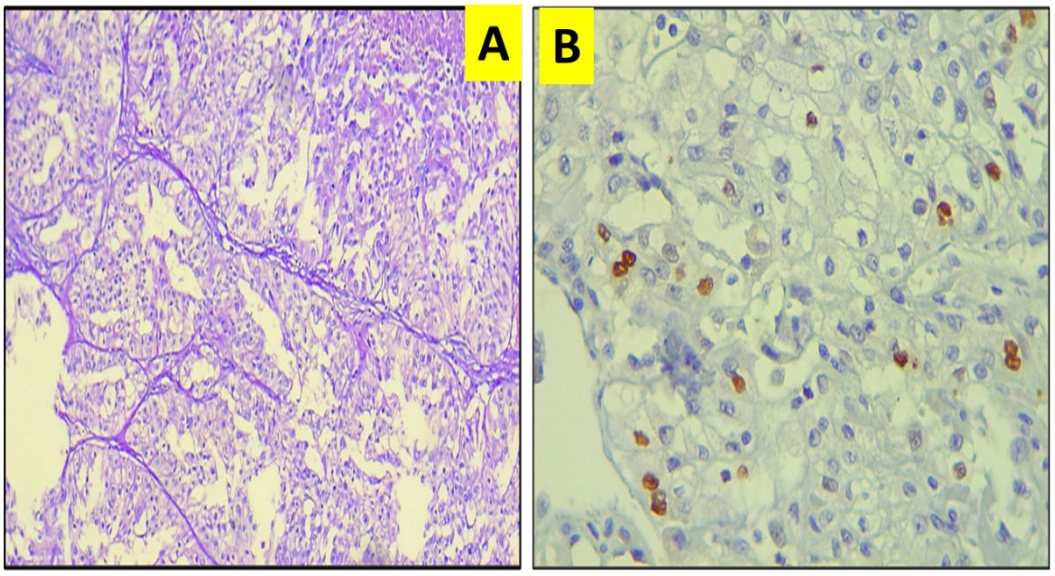

Figure 1. Histopathological and immunohistochemical characteristics of clear cell renal cell carcinoma (ccRCC). (A) Hematoxylin and eosin (H&E) staining demonstrates the characteristic morphological features of ccRCC, including clear cytoplasm and distinct cell borders with prominent vasculature (original magnification ×100). (B) Positive p53 immunohistochemical expression showing nuclear staining pattern in tumor cells, indicative of p53 protein accumulation (original magnification ×400). Scale bars represent standard measurements for the respective magnifications.

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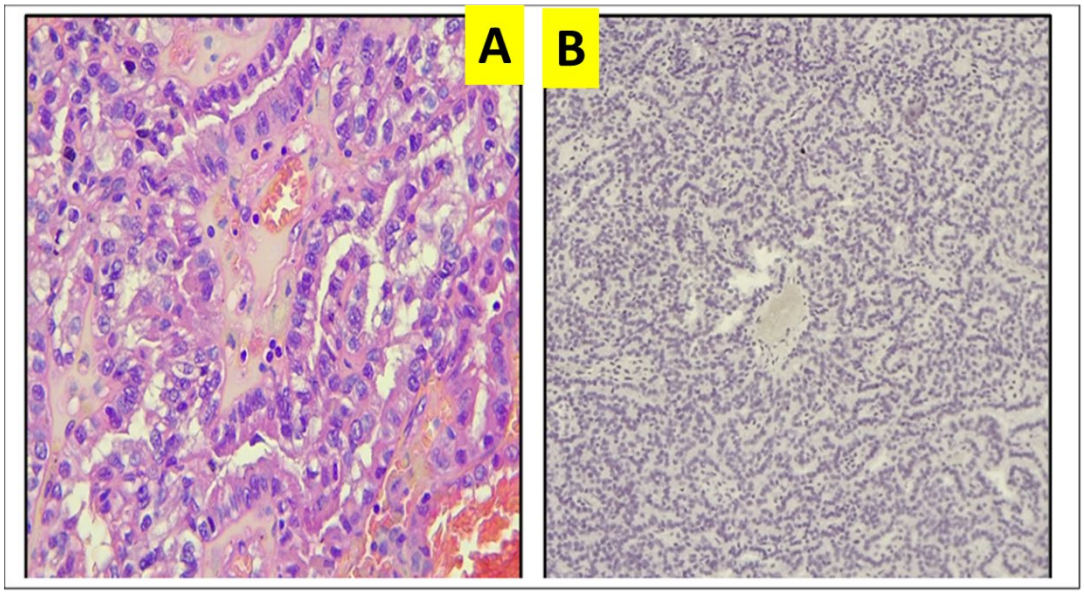

Figure 2. Histopathological and immunohistochemical characteristics of papillary renal cell carcinoma (pRCC). (A) Hematoxylin and eosin (H&E) staining reveals the characteristic papillary architecture with fibrovascular cores lined by cuboidal to columnar epithelial cells, demonstrating the typical morphological features of pRCC (original magnification ×400). (B) Negative p53 immunohistochemical expression showing absence of nuclear staining in tumor cells, indicating low p53 protein accumulation and wild-type p53 status (original magnification ×100). Scale bars represent standard measurements for the respective magnifications.

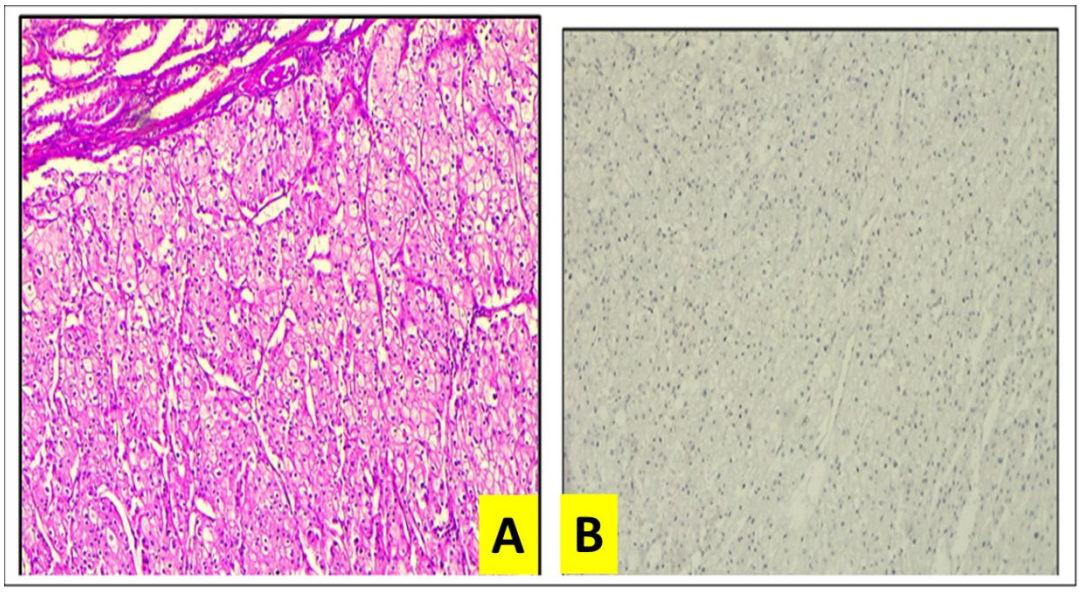

Figure 3. Histopathological and immunohistochemical characteristics of chromophobe renal cell carcinoma (chRCC). (A) Hematoxylin and eosin (H&E) staining demonstrates the distinctive morphological features of chRCC, including large

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polygonal cells with abundant eosinophilic cytoplasm, prominent cell membranes, and characteristic "plant cell-like" appearance (original magnification ×100). (B) Negative p53 immunohistochemical expression showing absence of nuclear staining in tumor cells, consistent with wild-type p53 status and indicating low p53 protein accumulation (original magnification ×100). Scale bars represent standard measurements for the respective magnifications.

In the analysis of the association between P53 expression and grade, tumors with grade (1 and 2) 37 cases (60.6%) showed No P53 expression, and only one case (25%) had positive expression. For tumors with grade (3 and 4), 24 cases (39.3%) exhibited No P53 expression, while three cases (75%) showed positive expression with P value was (0.299). In the evaluation of the relationship between P53 expression and LVI, among cases with LVI only two cases (50%) had positive expression with P value was (0.225).Regarding the association between P53 expression and the (pT stage), among cases classified as (T1 and T2), three cases (75%) had positive expression, and among cases classified as (T3 and T4) stage only one case (25%) exhibited positive expression with P value was (0.568). These data are demonstrated in table (2).

Table 2. The association between P53 immunohistochemistry expression and the clinicopathological parameters.

	Clinicopathological parameters	No expression		Positive expression		
		n.	%	n.	%	P-value
Age	< 55 years	26	42.6	1	25	0.635
	≥ 55 years	35	57.3	3	75	
Sex	Male	39	63.9	3	75	0.654
	female	22	36	1	25	
Site	Left	38	62.2	1	25	0.140
	Right	23	37.7	3	75	
Histopathological subtypes	Clear cell RCC	49	80	4	100	---
	Papillary cell RCC	9	14	0	0.0	
	Chromophobe RCC	3	4.9	0	0.0	
Grade	Grade 1and 2	37	60.6	1	25	0.299
	Grade 3 and 4	24	39.3	3	75	
Lymphovascular invasion	Absent	48	78.6	2	50	0.225
	Present	13	21.3	2	50	
pT stage	T1 and T2	37	60.6	3	75	0.568
	T3 and T4	24	39.3	1	25	

B. Discussion

In this current study the frequency of p53 expression in RCC cases was 6.2% only, the expression was low involving only four cases of all the sample size, which is

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consistent with the reported infrequent mutation of p53 in renal cell cancers [6-9]. P53 Staining was observed mainly in individual cells and occasionally in small cell group,. this goes in line with what Baytekin et al. observed in Turkey [10]. The frequency of P53 expression in the current study was inconsistent with Habib et al. in Baghdad/ Iraq (45%) [11], Al-Ali et al. in Najaf (Iraq) [12], (68.75%) Noroozinia et al. in Urmia (Iran) [13], (20.3%), Mombini et al. in Ahwaz (Iran) (45.4%) [14], Radovanović et al. in Belgrade (Serbia) (36.7%) [7] and Gupta et al. in Bengaluru (India) (66%) [5]. On the other hand Vasavada et al. in USA observed (0%) expression [15]. The wide variation from (0%-75%) in the frequency of P53 positive cases in those studies may be due to variation in IHC staining technical operation with different manufacture's variation as kits and types of antibodies which were used, different sample size, different scoring systems and cut-off points for immunostaining, fixation time, and in addition to the genetic and environmental factors in different population. The low expression of P53 in the current study is explained by the low rate of TP53 gene mutations in renal tumors. Li et al. performed a somatic p53 mutation analysis in the three major types of RCCs. They found that the mutation rate of TP53 is higher in chRCC (31.8%), while TP53 in ccRCC and pRCC (3.24%) and (2.48%) respectively, have a much lower mutation rate [6,9]. In regards to the age, (58.5%) of cases were 55 years and older, and this goes in line with the believe that RCC is more frequent in older aged individuals [16]. P53 immunexpression was found to be positive in (57.3%) of cases who were 55 years and older, No statistical association was found between P53 expression and age, which is consistent with Gupta et al. in India [5] and Noroozinia et al. in Iran [13].

Of the cases included in this research paper (64.6%) were males and (35.4%) were females, which supports the idea that the frequency of RCC is more common in males [16], and also goes in line with what Godlewski et al. observed in Poland and with what many other studies observed in various geographical areas [8], including Radovanović et al. in Belgrade (Serbia), Gupta et al. in Bengaluru (India), Mombini et al. in Ahwaz (Iran), Baytekin et al. in Izmir (Turkey), and Habib et al. Baghdad (Iraq) [7,8,10,11,14], in those studies RCC was observed in higher frequency in specimens obtained from men. In the present study (75%) and (25%) were positive for P53 in male and female population respectively. No statistical association was found between P53 expression and sex which is consistent with Noroozinia et al. Iran [13]. Most of the RCC cases included in this study affected the left kidney (60%). P53

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expression frequency was higher with cases that involved the right kidney (75%).In the present study (ccRCC) was the most common RCC subtype accounting for (81.5%) followed by pRCC (13.8%) and finally chRCC (4.6%), this is consistent with Gupta et al. in India [5], Hodorova et al. in Slovak Republic [17], Noroozinia et al. in Iran [13] and Mombini et al. in Iran [14]. The (6.2%) of cases that were positive for P53 were only of (ccRCC) subtype and No expression was found in the other two subtypes of the sample cases, this goes against what Gupta et al. observed in India [5] and Mombini et al. in Iran [14], in both studies the frequency of P53 expression was high in (ChRCC) followed by (pRCC) and lastly in (ccRCC).In analysis of grade, most sample cases were grade 2 (49.2%), which goes in line with Habib et al. in Iraq [11], Baytekin et al. in Iran [10] and contradicts Gupta et al. in India [5], and Zheng et al. in China [19]. Cases with grade 3 and 4 showed highier frequency for P53 expression (75%) this was consistent with Uhlman et al. in the USA [18], in which positive staining was associated with high grade. In analysis of LVI (76.9%) of cases showed No LVI, and of these only (50%) showed P53 positivity, and of the (23.1%) cases that showed LVI (50 %) showed P53 expression. There was No statistical association was observed between P53 expression and LVI. Regarding the (pT) stage most of the cases in the sample selected were (pT1a) and (pT3a) which is inconsistent with Gupta et al. in India [5] and Habib et al. in Iraq in both the most frequent (pT) stage was (T2a) [11]. P53 expression frequency was high in cases with (pT1,pT2) stage. No statistical association between P53 expression and (pT) stage was observed which is consistent with Zheng et al. [19] in China and Gupta et al. in India [5] and contradict Radovanović et al. in Slovak republic [7], and Godlewski et al. in Poland [8].

Conclusions

Positive P53 expression was found in (6.2%) of the study sample. The positive cases were mainly of male gender and aged 55 years and older. All positive cases were of (ccRCC) subtype. The positivity mainly involved tumors with grade (3 and 4), stage (T1 and T2) and (50%) of the cases which were positive for lymphovascular invasion. No significant statistical association was observed between P53 expression and the clinicopathological parameters studied.

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