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The Dysregulation of Cyclin Dependent Kinase Regulators Role in SV40 Related Renal Cell Carcinoma

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Original Research Article

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ABSTRACT

The purpose of this study was to explore the possible involvement of SV40 polyomavirus in the development of renal cell carcinoma (RCC) in patients from the province of Al-Najaf. The study analyzed 75 paraffin-embedded block tissues of RCC, collected from archives of AL-Sader Medical City, and some private histopathology laboratories in Najaf governorate. The patients included 45 males and 30 females, aged between 22 and 70 years. The study used advanced scientific techniques, including Polymerase Chain Reaction (PCR) and immunohistochemistry (IHC), to detect the presence of SV40 and evaluate the expression state of Cyclin-Dependent Kinase Regulators (KAP or cyclin-dependent kinase inhibitor 3 (CDKN3) & Cyclin E1 markers). Hematoxylin and Eosin staining was used for diagnosing RCC. The study found that RCC is associated with the dysregulation of Cyclin-Dependent Kinase regulators (CDK), caused by the SV40 polyomavirus. The results of the IHC analysis showed an increased positive percentage for KAP or CDKN3 marker and a decreased positive percentage of Cyclin E1 marker. Additionally, the clear cell type was found to be the most common, accounting for 56% of the cases, while grade I was the most prevalent, representing 41.3% of the cases. Tumor stage type I was found to be higher, with 25 cases. PCR detected the presence of SV40 in 20 cases, accounting for 26.7% of the

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total cases studied. The study concluded that the Simian Virus 40 (SV40), particularly its Large T Antigen (Tag), affects CDK regulators and disrupts the delicate equilibrium of cell cycle regulation systems. Therefore, the study suggests a possible link between the development of renal cell carcinoma and the SV40 polyomavirus. The study recommends routine testing for the detection of RCC using PCR and IHC methods.

Keywords: SV40; renal cell carcinoma; immunohistochemistry; PCR.

1. INTRODUCTION

Polyomaviruses (PyV) is recognized as a small, non-enveloped, double-stranded deoxyribonucleic acid, icosahedral symmetry with 5 kbp genomes, belonging to *polyomaviridae* family. The term polyomavirus (PyV) comes from Greek origin, where poly- indicate numerous and -oma which denote tumors, was belong to *Papovaviridae* family, an abbreviation suggested via Melnick, as well as gained via combing the names of the following viruses represented by '*Pa*pilloma', *'Po*lyoma', and *'Va*cuolating' (Dalianis and Hirsch, 2013).

The detection of Simian virus 40 SV40, was reported within 1960 when millions of populations in Africa, Europe, Canada, Asia and North and South America were inoculated from both in-activated and a live polio-vaccines, initiate to be infected by Simian virus 40 [1].

SV40 genome is circular ds DNA, which encodes for 6 proteins: three structural proteins (including VP-1; VP-2 and VP-3, which are structural proteins allow genetic material to be accumulated in SV40 virion [2], 2 proteins important for the life cycle, that induce replication of SV40, gene-expression, in addition to entry of S phase and DNA synthesis, by this means inducing cycle development (large "T" antigen plus small "t" antigen oncoproteins) [3] and 2 small proteins of unidentified function (the agnoprotein, which rule the perinuclear localize of "VP-1" throughout virion construction, after that induce assemblage of virion [4], and 17kT, which participate the majority of amino acid sequence with N terminal domain of T-ag, encourage progression of cell cycle in existence of t-Ag, as well as tumorigenic formation [5].

Simian virus 40 return to Polyomaviridae, genus Betapolyomavirus, which is strongly correlated to other types of polyomaviruses including JCPyV and BKPyV [6]. SV40 be capable of transmitted by diverse ways like sexual course and faecal-oral ways that are accountable for horizontal virus infection in peoples [7].

The infection of cell beginning by attachment capsid of SV40 to the cell surface by binding among VP-1, cell surface receptor ganglioside GM1 and the major histocompatibility complex class-I (MHC-I), which function as coreceptors and allow viral DNA to be contained within the SV40 virion, which is formed by 360 VP 1 molecules, comprising 72 pentamers [2].

This virus in nature infects specific species of Asian macaques, especially rhesus monkey. Sequences of SV40 were detected in samples of urine and stool as well as in both children and adults, this representing that the sexual and oro-fecal ways of spread that possible to accountable for horizontal SV40 infection in individuals [8,7].

On the other hand, the liberate of SV40 with no exhibit a cytopathic effect (CPE) found in particular types of cells, for instance human epithelial, fibroblasts, mesothelial and embryonic renal cell which points that kidney tissue can function as reservoir for SV40 in humans [9].

Expression of both T-Ag and t-Ag can cause elevated cell transformation professionally. In reality, Tag prohibit the actions of numerous diverse cellular factors concerned in differentiation, cell growth and the cell cycle, for instance p130, p300 and p400. As well as, T-Ag and t-Ag was prohibiting the activity of pRb and p53. These interconnections are obligatory so as to accomplish complete cell transformation in human [10].

The oncogenic role of polyomavirus was formerly related with a wide array of tumor types for instance malignant pleural mesothelioma (MPM) and bone [11], brain [12], lung [13], thyroid [14], pituitary [15], and urothelial [16] tumors, pleomorphic adenomas of parotid glands [17], ependymomas choroid and plexus tumors in youth [18]. Additionally, footprints from DNA of SV40 have been reported in breast [19] and colon carcinoma [20].

Table 1. The world health organization/International society of urological pathology grading system for clear cell and papillary renal carcinoma (WHO/ISUP, 2021)

Grade 1	Tumour cell nucleoli (absent/inconspicuous), basophilic at ×400 magnification
Grade 2	Tumour cell nucleoli (conspicuous), eosinophilic at ×400 magnification and evident but not prominent at ×100 magnification
Grade 3	Tumour cell nucleoli (conspicuous), eosinophilic at ×100 magnification
Grade 4	Tumour showing extreme nuclear pleomorphism, Tumour giant cells, the presence of any proportion of Tumour showing rhabdoid and/or sarcomatoid morphology.

Also, Tag of SV40 possibly causes transformation by stimulating mutations to the genome of cellular or numerical/structural variation of chromosomes, like gaps, breaks, ring and dicentric chromosomes, chromatid exchanges, translocations, duplications and deletions [21]. The major function of t-Ag in transformation is to link both subunits, catalytic (36 kDa) and regulatory (63 kDa) of protein phosphatase 2A (PP2A), in-activating role [22].

1.1 Grading Renal Cell Carcinoma

Patients distributing according grading of The World Health Organization (WHO)/International Society of Urological Pathology.

2. METHODS

This present study was planned as cross-section study to detect SV40 with renal cell carcinoma and includes 75 (45 males and 30 females, whose ages ranged from 22 to 70 years) paraffin impeding block tissues of renal cell carcinoma from archives of AL-Sader Medical City and some archives of private histopathology laboratories in Najaf governorate. The data are from January 2016 to the December of the same year by using Polymers Chain Reaction for detection of DNA SV40 and immunohistochemistry technique for detect expression state of Cyclin Dependent Kinase Regulators (KAP or cyclin-dependent kinase inhibitor 3 (CDKN3) & Cyclin E1 markers), using Hematoxylin and Eosin stain for diagnosis of RCC.

3. RESULTS

Increased positive percentage for KAP or CDKN3 marker and decreased positive percentage of Cyclin E1 marker were seen in the results of the Immunohistochemistry technique (IHC). As well, found that clear cell type was higher with 42 (56%), grade I was higher with 31 (41.3%) and tumor stage type I was higher (25). The positive results by PCR techniques in RCC patient showed that 20 (26.7% out of 75 cases) of block tissues.

3.1 Clinicopathological Analysis

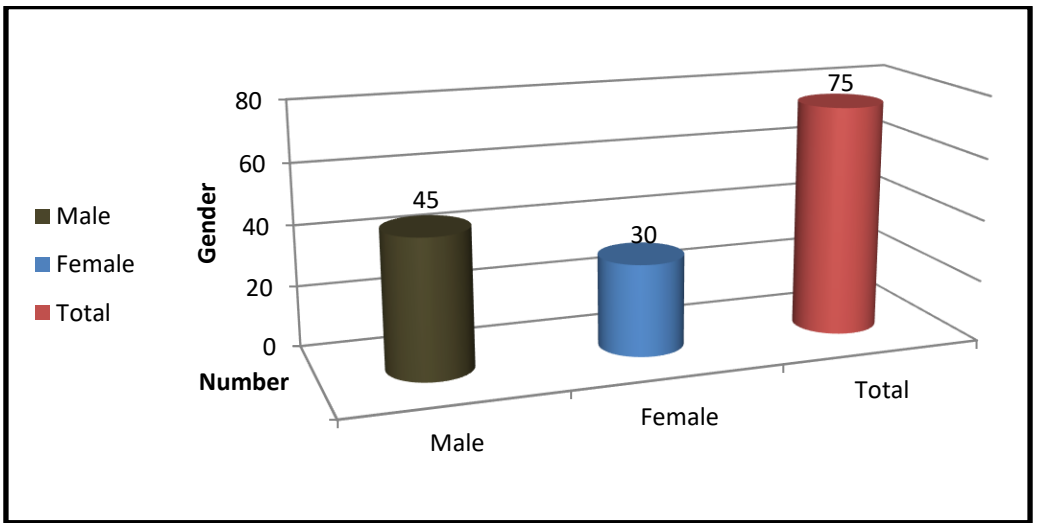

Fig. 1. Distribution of RCC patients according to gender

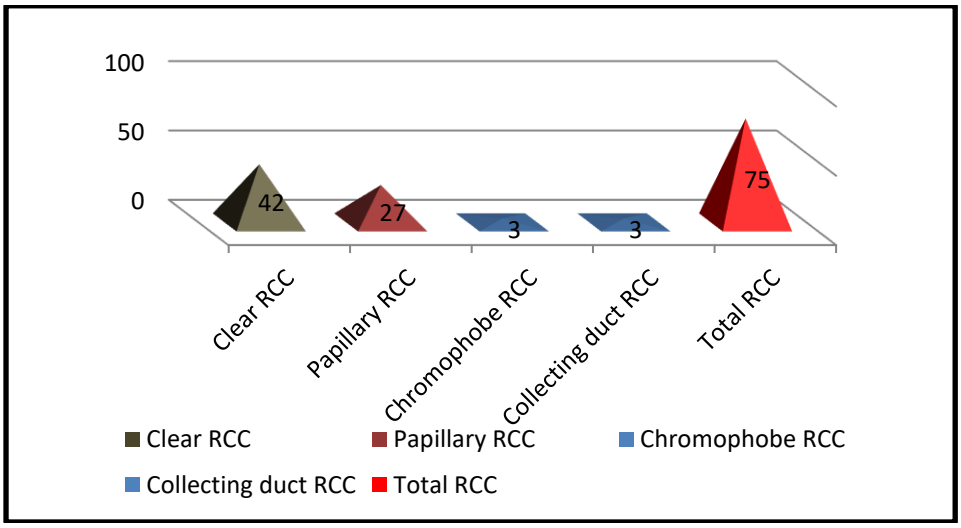

Fig. 2. Distribution of RCC patients according to histological types

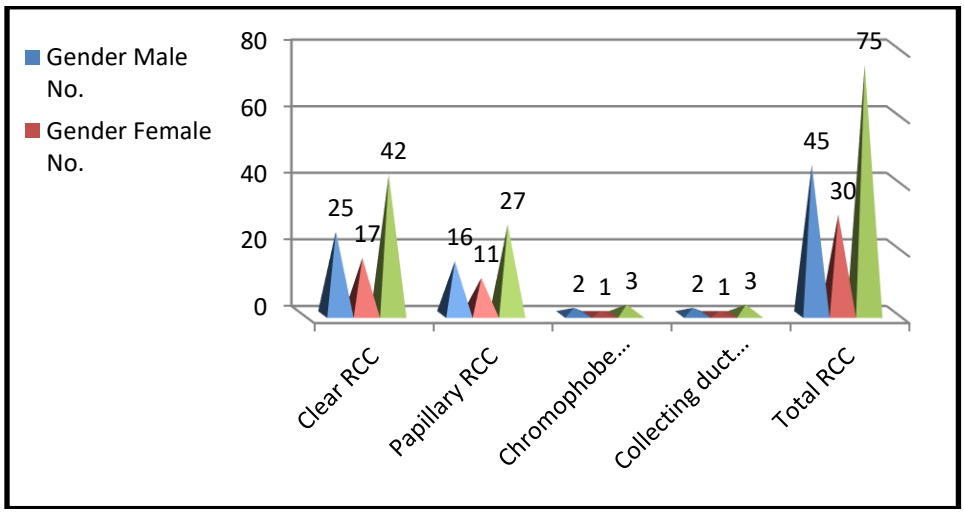

Fig. 3. Distribution of RCC patients according to their histopathological types and gender

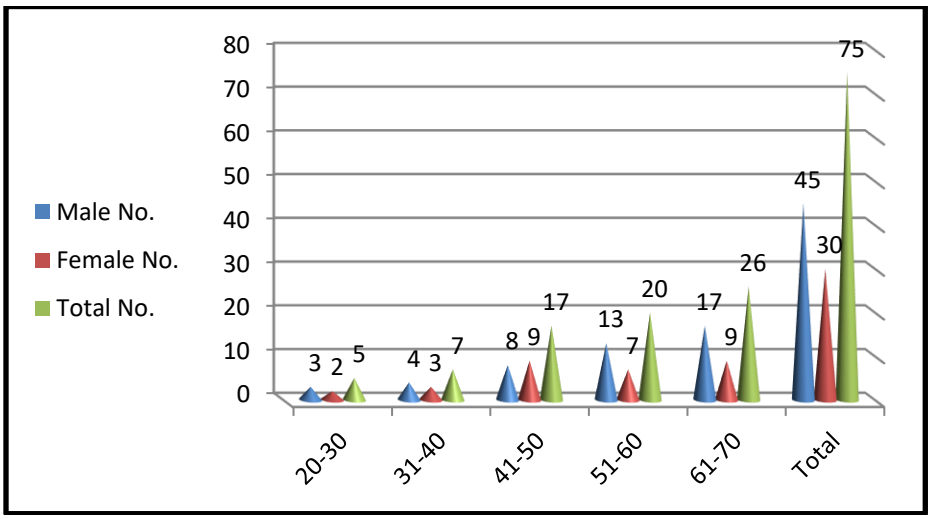

Fig. 4. Distribution of RCC patients according to their gender and age

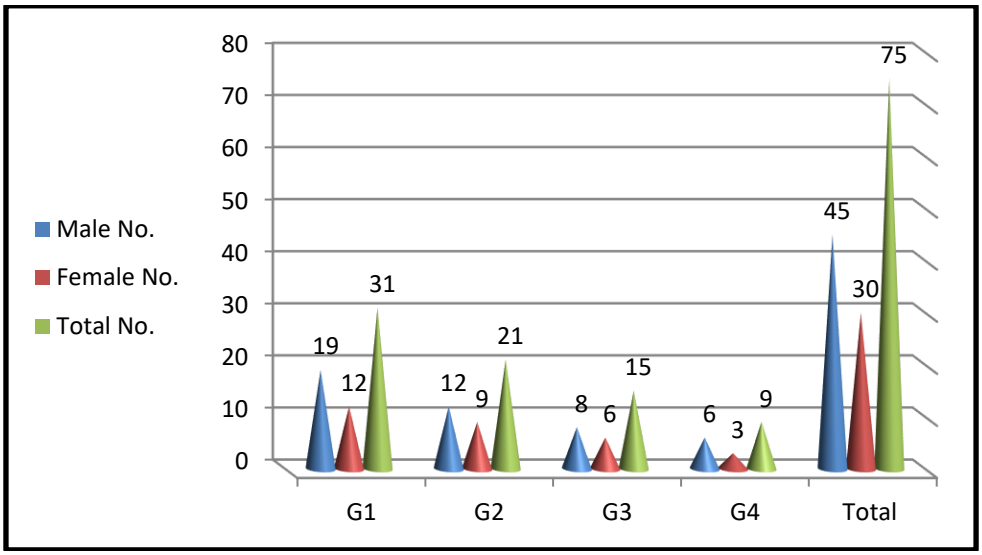

Fig. 5. Distribution of RCC patients according to their Gender and Grading Systems

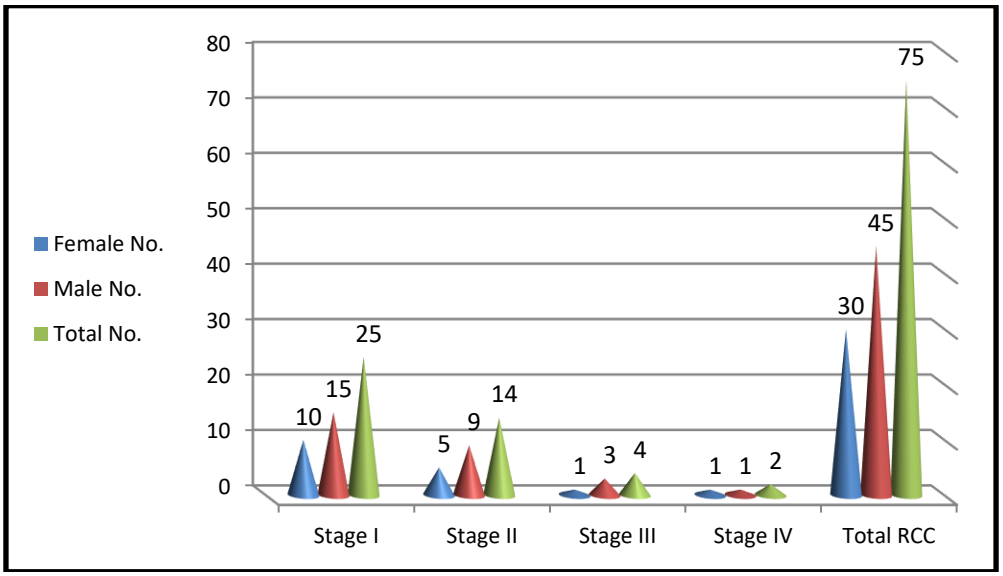

Fig. 6. Distribution of RCC patients according to their gender and pathological tumor stage

3.2 Immunohistochemical Analysis (Cyclin E1 & CDKN3)

In the this study, the results of IHC by utilizing EnVisionTM FLEX stain revealed a brownish discoloration of nucleus or nucleoplasm for Cyclin E1 whereas in CDKN3 was staining the cytosol or cytoplasm, as showed in Figs. (7-9).

4. DISCUSSION

In this study, the existence of SV40 in blocked tissue taking from 75 patients suffering from RCC, it uses molecular technique involving PCR technique for detection of SV40 DNA united with immunohistochemistry technique (IHC) which are significant to verify the existence of Simian virus 40.

Simian virus 40 (SV40) define as a monkey virus which by accident entered to man, in 1955-1963 years, throughout polluted polio-virus vaccines that found the transforming and oncogencity actions of T-Ag and t-Ag of this virus, which provoked examination of SV40 in humans' cancer. Generally, it is thought that contamination of polio vaccines was consider the major cause of infection with SV40 in humans, nearly all researches have defined exposure of SV40 founded on vaccination [23].

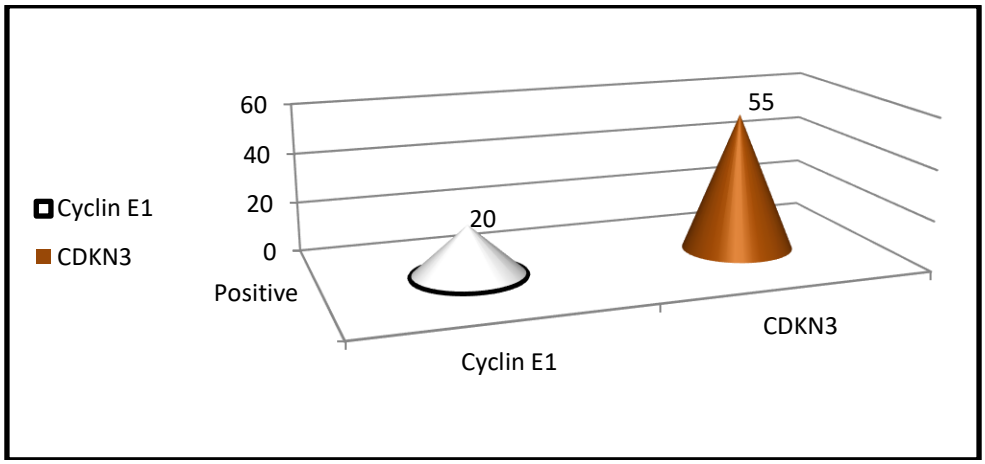

Fig. 7. Circulation of Cyclin E1 and CDKN3 by using IHC.

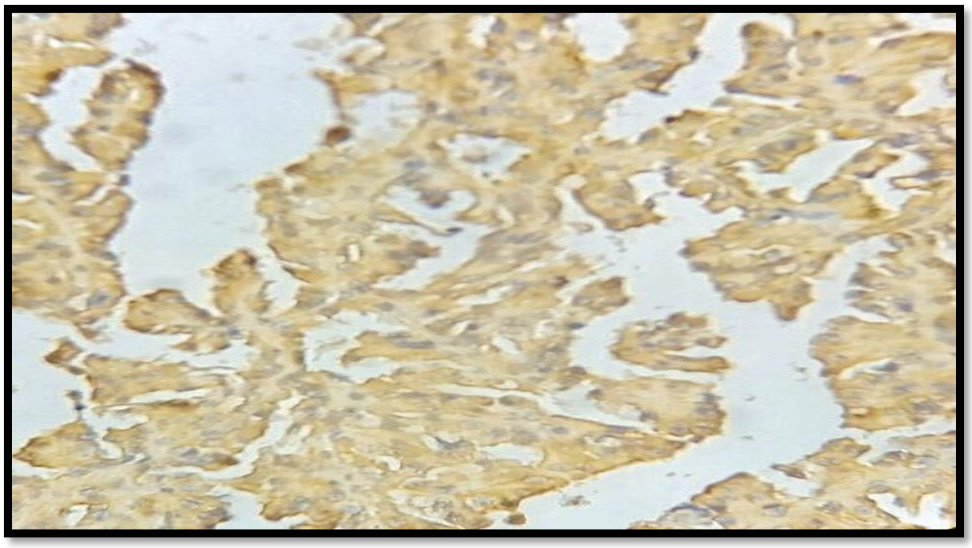

Fig. 8. Negative cyclineE1 stain of papillary type of RCC patients

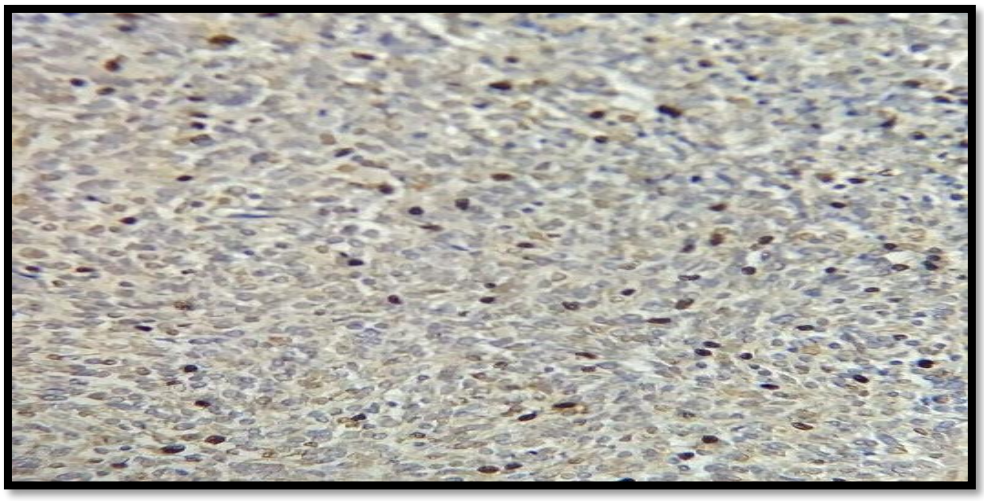

Fig. 9. Sarcomatoid carcinoma positive strong cyclineE1 stain score 2 (10 X40)

Most studies demonstrate that the kidney can function as a reservoir for SV40 in individuals. The sequence of this virus was reported in renal tissue and cells of urine sediments suffering from RCC [24] like Garcea and Imperiale, [22] who found that SV40 causes infection in renal cells somewhere might possibly reactivation by immunosuppression. Also, Vanchiere et al., [7] reported that discovery of SV40 in renal tissue of human which indicates that kidney represented a position of viral latency, similar to in the usual simian host.

Bofill-Mas et al., [25] does not discover SV40 sequences in any tissue of RCC combine in diverse geographic regions of Europe and South Africa, while other types of polyomavirus's sequences were detected from the majority of these tissues. In contrast to Manfredi et al., [26] who have failed to discover the sequences of SV40 in these tumors.

In molecular technique involving PCR, it was found that only 20 of 75 paraffin-embedded block tissue yielded SV40 for the reason that only extremely little amounts of these tissue block were offered for investigation, it was inspiring that DNA of SV40 recognized from 75 renal block tissue. The likelihood of occasional laboratory pollution of tissue block was excluded due to genetic material (DNA) linked with cancer and DNA of SV40 from laboratory progeny diverge sequences both within the viral regulatory area and at the carboxy terminus of T-Ag [27].

Some reports have lacking proof that SV40 was causation significant in the progression of human cancer but, Butel and Lednicky, [28] reported that the presence of the DNA of SV40 will suggests that the opportunity of these virus in the genesis of some RCC in human.

Bergsagel et al. [18] have revealed that negative SV40 outcome in renal tumor possibly because of utilize of few technical approaches. Also similarly, Leithner et al., [29] and Priftakis et al., [30] have recorded that never detected the sequences of SV40 in both Austria and Turkey, as in Sweden. While the predominance of SV40 DNA that are revealed in these cancers was diverse country for instance in Germany and Hungary [31].

Various repots recorded by Lopez-Rios et al., [32] showing that positive sequences of SV40 DNA by PCR technique as well as Mayall et al., [33] and Aoe et al., [34] reported that negative results by using quantitative PCR assay.

In general Iraq is considered as one of various countries in the Middle East regions that have special exciting to renal cell carcinoma and which regarded as the second mainly frequent urological malignancy [35]. As a result, it is found the elevated proportion of males than females have in agreement with many studies finished by Vikram et al., [36] and Mahasin et al., [37].

Renal cell carcinoma is the majority frequent malignancy of kidney, as well as can classified into five types including ccRCC, pRCC, chRCC, cd RCC and unclassified types. It is found in the presented study the most frequent type was clear cell RCC (42 of 75) which concordance with repots accomplished by Aiman et al., [38] and Mahasin et al., [37].

By using TNM classification of malignant tumors of RCC rely on the American Joint Committee on Cancer (AJCC), Stafford et al., [39] recorded that males' patients have higher stage tumors while females' patients have lower stage cancers, this is in concordance with our study. When in examination of the Fuhrman nuclear grade, Mukhopadhyay et al., [40] have discovery higher frequency of Grade 1 and lower frequency of Grade 3 and Grade 4.

The most common age group in their study is 61-70 years followed by 51-60 years. These results are in conformity with numerous reports such Noroozinia et al., [41], Khafaja et al., [42] and Hassan et al., [43] while unlikeness with Latif et al., [44] and Takure et al., [45].

In immunohistochemical technique, the immunohistochemical indicators are significant in identifying RCC patients that are investigated by the EnVision System, this is agreement with the report done by Lai et al., [46] who have recorded that a elevated expression of CDKN3 in renal tissues whilst Bisteau et al., [47] have found that tough expression of cyclin E1 which is related with poor prognosis of patients.

Also, Brousset et al., [48] have unsuccessful to discover Tag of SV40 in these tumors by using immunohistochemistry technique with a extremely sensitive technique in spite of actuality that recorded in experienced tissues have DNA sequences of SV40.

The results of analysis of DNA SV40 polyomavirus by PCR in patient with RCC as; the total number of positive results of PCR is 20 (26.7%) whilst the negative results of PCR are 55 (73.3%).

5. CONCLUSION

Renal cell carcinoma (RCC) is a complex and heterogeneous disease that is associated with a dysregulation of cyclin-dependent kinase (CDK) regulators. The CDK regulators play a crucial role in the regulation of the cell cycle, and any dysregulation can lead to the uncontrolled proliferation of cancer cells. Recent studies show that the Simian virus 40 (SV40) is responsible for the dysregulation of CDK regulators in RCC. SV40 has been identified as a potential oncogenic virus in humans, and its association with RCC has been established. The dysregulation of CDK regulators in RCC associated with SV40 is a complex molecular pathway that involves the interaction between the viral proteins and host cell pathways. The findings of this study have expanded our knowledge of the condition. It has been suggested that the creation of tailored treatments meant to counteract SV40-related RCC by reestablishing the equilibrium of cell cycle regulation is possible. These treatments could target the CDK regulators and the mechanisms by which the virus interacts with the host cell pathways, thus leading to the restoration of normal cellular function. In conclusion, this study has shed light on the complex molecular pathways involved in the etiology of RCC associated with SV40. The findings have opened the door for the creation of targeted treatments meant to restore the equilibrium of cell cycle regulation and counteract the dysregulation caused by the virus. This has the potential to significantly improve the prognosis of patients with SV40-related RCC.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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