ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2022 January 25; 11(1): 1-38

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Bimonthly Volume 11 Number 1 January 25, 2022

OPINION REVIEW

REVIEW

ORIGINAL ARTICLE

Retrospective Study

World Journal of Nephrology

Bimonthly Volume 11 Number 1 January 25, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Aristeidis Stavroulopoulos, MD, Chief Medical Officer of Pan Health Group, Ploutarchou 4, Athens 10675, Greece; Director of the Athens Kidney Institute Nephroexpert, Christovasili 3, Athens 14562, Greece

AIMS AND SCOPE

The primary aim of *World Journal of Nephrology* (*WJN*, *World J Nephrol*) is to provide scholars and readers from various fields of nephrology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc*.

INDEXING/ABSTRACTING

The *WJN* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Li Zuo, Ying-Yong Zhao

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-6124/editorialboard.htm

PUBLICATION DATE
January 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2022 January 25; 11(1): 1-12

DOI: 10.5527/wjn.v11.i1.1

ISSN 2220-6124 (online)

OPINION REVIEW

Renal cell carcinoma and viral infections: A dangerous relationship?

Melissa Bersanelli, Chiara Casartelli, Sebastiano Buti, Camillo Porta

ORCID number: Melissa Bersanelli 0000-0002-6527-6281; Chiara Casartelli 0000-0001-6476-6871; Sebastiano Buti 0000-0003-0876-0226; Camillo Porta 0000-0003-2412-1563.

Author contributions: Bersanelli M and Porta C conceptualized the work; all authors contributed to the article's writing and revision.

Conflict-of-interest statement: No funding was provided for the present study. No acknowledgments. Melissa Bersanelli received honoraria as a speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, AstraZeneca, Pierre Fabre, and Pfizer and as a consultant for advisory role by Novartis, BMS, IPSEN, and Pfizer; she also received fees for copyright transfer by Sciclone Pharmaceuticals and research funding by Roche S.p.A., Seqirus UK, Pfizer, Novartis, BMS, Astra Zeneca, and Sanofi Genzyme. Chiara Casartelli has no conflicts of interest to disclose. Sebastiano Buti received honoraria as a speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca and Novartis; he also received research funding from Novartis. Camillo Porta received honoraria a Consultant or Speaker for Angelini, Astra Zeneca, BMS, Eisai, EUSA, General

Melissa Bersanelli, Chiara Casartelli, Sebastiano Buti, Medical Oncology Unit, University Hospital of Parma, Parma 43126, Italy

Melissa Bersanelli, Chiara Casartelli, Department of Medicine and Surgery, University of Parma, Parma 43126, Italy

Camillo Porta, Department of Biomedical Sciences and Human Oncology, University of Bari 'A. Moro', Bari 70121, Italy

Camillo Porta, Department of Medical Oncology, Policlinico Consorziale, Bari 70124, Italy

Corresponding author: Melissa Bersanelli, MD, Adjunct Professor, Postdoctoral Fellow, Staff Physician, Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, Parma 43126, Italy. bersamel@libero.it

Abstract

Virus-related cancers in humans are widely recognized, but in the case of renal cancer, the link with the world of viruses is not clearly established in humans, despite being known in animal biology. In the present review, we aimed to explore the literature on renal cell carcinoma (RCC) for a possible role of viruses in human RCC tumorigenesis and immune homeostasis, hypothesizing the contribution of viruses to the immunogenicity of this tumor. A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords "*virus*" or "*viruses*" or "*viral infection*" matched with ("AND") "*renal cell carcinoma*" or "*kidney cancer*" or "*renal cancer*" or "*renal carcinoma*" or "*renal tumor*" or "*RCC*". The retrieved findings evidenced two main aspects testifying to the relationship between RCC and viruses: The presence of viruses within the tumor, especially in non-clear cell RCC cases, and RCC occurrence in cases with pre-existing chronic viral infections. Some retrieved translational and clinical data suggest the possible contribution of viruses, particularly Epstein-Barr virus, to the marked immunogenicity of sarcomatoid RCC. In addition, it was revealed the possible role of endogenous retrovirus reactivation in RCC oncogenesis, introducing new fascinating hypotheses about this tumor's immunogenicity and likeliness of response to immune checkpoint inhibitors.

Key Words: Renal cell carcinoma; Renal cancer; Kidney cancer; Viruses; Viral infections; Retrotransposons

Electric, Ipsen, Janssen, Merck, MSD, Novartis and Pfizer, acted as an Expert Testimony for EUSA and Pfizer, and was a Protocol Steering Committee Member of BMS, Eisai, and EUSA. Finally, he did receive travel support from Roche.

Country/Territory of origin: Italy

Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: July 31, 2021
Revised: August 10, 2021
Accepted: December 2, 2021
Article in press: December 2, 2021
Published online: January 25, 2022

P-Reviewer: Hasan A
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

Core Tip: An overview of the complex interplay between viral agents and renal carcinogenesis, possibly influencing the course of the disease, the tumor immune microenvironment, the production of new antigens, the host's and the tumor's immunogenicity, and, even more, the response to immune checkpoint blockade.

Citation: Bersanelli M, Casartelli C, Buti S, Porta C. Renal cell carcinoma and viral infections: A dangerous relationship? *World J Nephrol* 2022; 11(1): 1-12
URL: https://www.wjgnet.com/2220-6124/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.5527/wjn.v11.i1.1

INTRODUCTION

Virus-related cancers in humans are widely recognized and listed by the American Cancer Society[1]. The growing knowledge about the role of viruses as a cause of tumors has led to vaccines' development to prevent specific types of human cancers, which effectiveness is often prevented by prior exposure to the wild virus. Viruses known to be directly related to cancer are the human papillomaviruses (HPVs), leading mainly to cervix cancer and other genital or oral cancers; the Epstein-Barr virus (EBV), related to nasopharyngeal and gastric cancers, but also Burkitt and Hodgkin lymphomas; the human herpesvirus 8 (HHV8), associated with Kaposi sarcoma; the hepatitis B and C virus (HBV and HCV), provoking hepatocellular carcinoma, and even the human immunodeficiency virus (HIV) and HHV8, sometimes directly and often indirectly (through immunosuppression) related to a higher risk of developing Kaposi sarcoma, cervical cancer, tumors of the central nervous system and Hodgkin lymphoma[1].

In the case of renal cancer, the link with the world of viruses is established in animal biology, given the cause-effect relationship between the renal carcinoma of leopard frogs (*Rana pipiens*) and the Lucké tumor herpesvirus (LTHV). In 1974, the Koch-Henle postulates between LTHV and frogs' renal cancer were fulfilled, demonstrating that (1) The agent was associated with the disease; (2) The agent induced the same disease in a susceptible host; (3) The agent was isolated from the induced disease; and (4) The isolated agent was the same agent originally associated with the disease[2]. Then, in 1982, LTHV was found in the primary tumor and metastatic tumor cells in the liver, fat body, and bladder, revealing both by histopathology and electron microscopy that the virus was retained from the primary tumor to its metastatic cells[3].

Given this ancestral link, we aimed to explore the literature on human renal cancer, namely renal cell carcinoma (RCC), to verify the possible role of viruses in human RCC tumorigenesis and immune homeostasis with the host.

In addition, considering the recent advances in the field of systemic immunotherapies, with the evidence of the efficacy of anti-programmed death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and anti-CTLA-4 immune checkpoint inhibitors (ICIs) in the treatment of metastatic RCC (mRCC)[4-7], we postulated the possible contribution of viruses to the immunogenicity of this tumor. While an "inflamed" phenotype characterizes other immunogenic tumors, RCC has been defined as a tumor with a prominent dysfunctional immune cell infiltrate[8]. Its immunogenicity is not entirely attributable to an inflamed status or a high tumor mutational burden, another recently identified element responsible for immune responsiveness[9]. Indeed, enigmatic genomic clusters of RCC have been identified as good responders to ICI-based treatment regimens despite very low mutational burden and apparently non-immunogenic features. This is the case of the so-called "Cluster 7", characterized by increased expression of small nucleolar RNAs (snoRNAs), guiding chemical RNA modifications, especially SNORDs[10,11].

The possibility that the presence of viruses in cancer cells could contribute to tumor immunogenicity is already suggested by the outstanding efficacy of immune checkpoint blockade in a tumor well-known to be highly resistant to standard anticancer therapies, namely Merkel cell carcinoma (MCC)[12]. MCC is a rare and aggressive skin cancer belonging to the family of neuroendocrine tumors, characterized by small cell features non-dissimilar to that of small cell lung cancer (SCLC). Despite the well-known unresponsiveness of neuroendocrine tumors to ICIs, recently non-effortlessly introduced in SCLC's treatment algorithm, MCC is counted among the

solid tumors which the new immunotherapy has changed history. Unlike other neuroendocrine tumors, MCC is associated, in 80% of cases, with the Merkel cell polyomavirus (MCPyV). The MCPyV small T oncoprotein can inactivate p53 and contributes to metastatic progression.

Interestingly, similarly to Cluster 7 described for RCC, MCPyV-positive cases bear a much lower mutational load, notwithstanding their immunogenicity[13]. Other than an increased neoantigens' production, this immune responsiveness might be due to the viral agent's contribution to shaping a peculiar tumor immune microenvironment (TIME), likely crucial to defining tumor immunogenicity. Recent findings support this hypothesis, showing that MCPyV presence, found in 101/176 analyzed cases of MCC, was related to changes in the tumor morphology, the density of the inflammatory infiltrate, the phenotype of the neoplastic cells, and the cell composition of the tumor stroma[14]. This evidence suggests that the presence of a virus can enhance inflammation within a tumor.

Given the emerging link between inflammation and ICI responsiveness, we hypothesized that a viral agent could contribute to rendering a tumor inflamed, on the one hand shaping the TIME, and on the other hand providing a more considerable amount of non-self-antigens, finally triggering a more potent immune response. In this view, the possible involvement of viruses in RCC oncogenesis and progression becomes an issue of interest, animating our aim to collect and describe evidence supporting this hypothesis.

LITERATURE SEARCH

A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords "*virus*" or "*viruses*" or "*viral infection*" matched with ("AND") "*renal cell carcinoma*" or "*kidney cancer*" or "*renal cancer*" or "*renal carcinoma*" or "*renal tumor*" or "*RCC*". The topics included in the literature selection were viruses in RCC, and RCC in patients with chronic viral infections. The use of oncolytic viruses for therapeutic purposes in RCC was an excluded topic. Other relevant issues close to the topics of interest that emerged from the literature screening were furtherly retrieved, and relevant publications were discussed.

ISSUES EMERGED: A THREE-FACED JANUS

Our search for possible links between viruses and RCC brought out two main aspects of their relationship: The presence of viruses within the tumor, and RCC occurrence in cases with pre-existing viral infections, both events documenting a potential causality effect. In addition, our multidirectional review unrevealed the possible role of endogenous retrovirus (ERV) reactivation in RCC oncogenesis, introducing new fascinating hypotheses about this tumor's immunogenicity.

ROLE OF VIRUSES IN RCC: HISTOPATHOLOGICAL FINDINGS

The research of histopathological findings testifying the presence of viruses in RCC allowed the retrieval of five retrospective publications[15-19]. These studies identified the virus within the tumor tissue through heterogeneous assays, demonstrating the viral presence at a rate of tumor specimens ranging from 7% to 30% of the case series analyzed. Contrariwise, the same viruses were present in the respective control specimens (healthy kidney or peritumoral tissue) at a rate ranging from 0% to 4%. Table 1 summarizes the relevant data, showing HPV, EBV, and BKV polyomavirus among the viruses identified.

The role of BKV polyomavirus was already known in the field of renal transplants. About 75%-90% of healthy adults are BKV seropositive, but the virus is likely to remain non-pathogen in most cases. Immunosuppressive therapies trigger the reactivation of BKV and graft nephropathy (BKVN) in organ transplant recipients. The treatment of biopsy-proven BKVN consists of the reduction of immunosuppressive drugs. Of note, Neirynck *et al*[17] reported a case of complete remission of metastatic sites from RCC after the allograft surgical removal and immunosuppressive treatment discontinuation, suggesting the key role of BKV in a case of RCC occurred five years after renal transplant[16].

Table 1 Studies about viruses in renal cell carcinoma

Ref.	Study type	Analyzed specimens		Virus investigated	Analysis method	Positive specimens	
		No. of cases and tumor type	No. of controls and tissue type			No. of positive cases and tumor type	No. of positive controls and tissue type
Kim *et al*[18], 2005	Retrospective	73 RCC (22 clear cell; 18 papillary; 20 chromophobe; 10 sarcomatoid; 3 oncocytoma)	18 non-neoplastic kidneys	EBV	EBER-ISH and PCRs (for EBNA-1 and EBNA-3C)	5/73 (all sarcomatoid histology) (EBER-ISH)[2]; 4/73 (all sarcomatoid histology) showed amplification of EBNA-1	0/18
Neirynck *et al* [17], 2012	Case report	1 RCC[1]	1 peritumoral tissue	BKV	IHC (for SV40 T antigen)	65%-70% neoplastic cells	< 1% non-neoplastic cells
Salehipoor *et al*[19], 2012	Retrospective	49 RCC	16 non-neoplastic kidneys	HPV; EBV; BKV; JCV	Nested PCR (virus DNA)	7/49 HPV (5 clear cell; 1 chromophobe 1 mixed type) 0 EBV, BKV JCV	0/16
Bulut *et al* [16], 2013	Retrospective	50 RCC	45 non-neoplastic kidneys	BKV	Nested PCR (BKV DNA) and RT-PCR (BKV mRNA)	10/50 (Nested PCR) 8/50 (RT-PCR)	2/45 non neoplastic kidneys (nested PCR, RT-PCR)
Farhadi *et al* [20], 2014	Retrospective	122 RCC (77 conventional; 26 papillary; 14 chromophobe; 1 collecting duct; 4 unclassified)	96 peritumoral tissues, 19 non-neoplastic kidneys	HR-HPV	Nested PCR (HR-HPV DNA). IHC (for p16INK4a and L1 Capsid Protein); CSAC-ISH	37/122 (17 clear-cell; 13 papillary; 4 chromophobe; 3 unclassified) (PCR). 24/118 (IHC for p16INK4a[3]) 0/118 (IHC for L1 capsid protein); 18/122 (CSAC-ISH)	4/96 peritumoral tissues; 0/19 non-neoplastic kidneys (PCR); 16/94 peritumoral tissue (IHC for p16INK4a); 0/94 peritumoral tissue (IHC for L1 capsid protein); NA (CSAC-ISH)

[1]Allograft kidney.

[2]EBER-positive signals were located only in the tumor-infiltrating lymphocytes.

[3]Human papillomavirus capsid protein.

RCC: Renal cell carcinoma; BKV: BK virus; EBV: Epstein-Barr virus; HPV: Human papillomavirus; JCV: JC virus; HR-HPV: High-risk human papillomavirus; Nested PCR: Nested polymerase chain reaction; RT-PCR: Real-time polymerase chain reaction; IHC: Immunohistochemistry; EBER-ISH: EBV-encoded RNAs in situ hybridization; EBNA-1 and EBNA-3C: EBV-encoded nuclear antigen 1 and EBV-encoded nuclear antigen 3C; CSAC-ISH: Catalyzed signal-amplified colorimetric in situ hybridization; NA: Not available.

From a different perspective, a critical role could be attributed to immunosuppression. Renal cancer occurs more frequently in renal transplanted patients than in the general population[20]. Considering the non-negligible rate of primary RCC in the allograft and the native kidney of renal transplant recipients, a possible synergy of immunosuppressive treatments and oncogenic viruses could be hypothesized as the basis of renal cancerogenesis in these patients[21]. According to a recent meta-analysis, renal transplant recipients were found to display a higher risk of all cancers, but their standard incidence ratio (SIR) was 10.77 (95%CI: 6.40-18.12; $P < 0.001$) concerning RCC, compared to an all-cancers SIR of 2.89 (95%CI: 2.13-3.91)[22].

Besides BKV evidence in the allograft, the role of this virus might be more extensive in renal cancer, given the significant association ($P = 0.03$) found between BKV DNA positivity of specimens and histological diagnosis of RCC (but not with that of urothelial carcinoma) in a cohort including 50 RCC, 40 urothelial cancers, and 65 non-cancer controls[15]. The levels of BKV mRNA were significantly higher in the RCC samples than in the control samples ($P < 0.05$), and the presence of BKV DNA resulted

in a 5-fold increased risk of RCC[15].

The limitations of the studies analyzed, beyond the limited sample size, are represented by the scarce homogeneity of investigational techniques, in the complete lack of validated assays to assess the viral presence within the tumor tissue. In most cases, the viral nucleic acid was detected by real-time polymerase chain reaction (PCR), but immunohistochemical techniques were also explored, with non-consistent results compared to the respective PCR in the same series[19].

Interestingly, a meaningful number of virus-positive cases were found in non-clear cell RCC (nccRCC) specimens, possibly subtending a different contribution in the etiopathogenesis between clear cell RCC (ccRCC) and non-conventional histologies. In the analyzed studies, Farhadi *et al*[20] found HPV in 13 of 26 (50%) papillary RCC specimens, compared to 17/77 ccRCC (22%) in the same series; similarly, Kim *et al*[18] found 50% of RCC with sarcomatoid histology positive for EBV. While the *VHL*-driven oncogenesis is widely recognized in ccRCC[23], less is known about the chain of oncogenic events in the case of nccRCC, a heterogeneous group of tumors with different histopathological, molecular, and clinical features, which are maybe promoted by shared stimuli.

EBV in sarcomatoid RCC: Is there a virus behind immunogenicity?

Sarcomatoid RCC (sRCC) is not considered a distinct histotype: Sarcomatoid dedifferentiation is a histological feature found in any RCC subtype, conferring aggressive behavior and a lower likelihood of response to antiangiogenic therapies when compared to ccRCC[24]. sRCC is characterized by the presence of spindle-shaped cells in a varying proportion of the tumor area, accounting for a sarcoma-like aspect, engaged in epithelial-mesenchymal transition and expressing mesenchymal markers. The differential diagnosis from retroperitoneal leiomyosarcoma or liposarcoma can be challenging in locally advanced cases. Nevertheless, opposite to these latter tumors, sRCC has been recently recognized as a highly immunogenic tumor, characterized by enriched immune signatures and high levels of tumor-infiltrating lymphocytes, likely to respond to ICI more than to antiangiogenic therapy[25]. From the molecular standpoint, sRCC exhibits a lower prevalence of PBRM1 mutations and angiogenesis markers, frequent CDKN2A/B alterations, and increased PD-L1 expression[26]. These findings have been applied to molecularly stratify patients, justifying improved outcomes of sarcomatoid tumors to checkpoint blockade *vs* antiangiogenics alone in first-line trials with ICI-based combinations, recently pooled in a meta-analysis[27].

In one of the previously cited histopathological research works, among 73 RCC specimens, EBV RNA was present in only 5 samples (6.8%)[17]. Curiously, all 5 EBV-positive tumors were sRCC. Considering the sRCC subgroup of samples, EBV-positive sRCC were 5 cases out of 10 (50%). Interestingly, EBV was located exclusively in the tumor-infiltrating B lymphocytes sRCC, clearly characterizing the TIME more than the tumor cells. These findings might suggest a possible contribution of viruses, in particular EBV, to the marked immunogenicity of sRCC, furtherly reiterated by recent subgroup analyses of new ICI-based combinations[28,29].

ERV REACTIVATION FROM PROMOTING RENAL CARCINOGENESIS TO PREDICTING IMMUNE RESPONSE

Approximately 40% of the mammalian genome is constituted by retrotransposons, archaic genic sequences introduced into the eukaryotic genome during the evolution, which can copy and paste themselves into different genomic locations through reverse transcription. Retrotransposons are epigenetically silenced in most somatic tissues and usually reactivated in early embryos. Their silencing is epigenetically provided through DNA methylation, histone methylation/acetylation, and posttranscriptional regulation. Mammalian retrotransposons include non-long term repeats (non-LTR) retrotransposons and LTR retrotransposons, the latter also known as ERVs[30]. Human ERVs (hERVs) are remnants of exogenous retroviruses integrated into the primate genome over evolutionary time. Besides LTRs, hERVs share other genomic similarities to other retroviruses, like *gag*, *pro*, *pol,* and *env* genes[31]. Their sequences are not transcribed in mRNA, but they can interfere with gene expression by antisense transcription or premature transcription termination, provide new transcription start sites changing gene regulation, contain regulatory elements on target genes, mediate genomic rearrangement through nonallelic homologous recombination[30].

Recent evidence reveals hERV reactivation in RCC, with LTRs exhibiting *HIF* binding and transcriptional activity in the RCC genome[32]. Some of these *HIF*-bound LTRs may function as distal enhancers inducing the expression of genes representing potential therapeutic targets in RCC.

ERV expression was shown to correlate with histone methylation and chromatin regulation genes in multiple cancer types, including ccRCC[33]. Eventually, ERVs provide an epigenomic mechanism for recurrent transcriptional signatures observed in RCC, suggesting that this tumor's epigenomic landscape might at least partially come from viruses.

Exaptation of promoters embedded within LTRs is emerging as a recurrent element of genomic dysregulation of oncogenesis, previously demonstrated in other cancers such as Hodgkin lymphoma, melanoma, and large B cell lymphoma. Recent research reported the first description of retroviral LTR exaptation in RCC, with distinct mechanisms from previous reports about this phenomenon[32]. Further evidence was provided on pan-cancer datasets by the Cancer Genome Atlas (TCGA): Using a previously compilated database of 3173 intact, full-length ERV sequences, Smith and co-investigators designed a computational workflow for identifying the expression of specific ERVs from RNA-sequencing and quantified ERVs expression in different tumors[31]. They evidenced that ccRCC contained the most significant number of prognostic ERVs among all cancer types encompassed, with shorter survival in patients with greater mean ERV expression (testifying a negative prognostic value).

As a further crucial step in this field, ERVs in RCC have recently been demonstrated predicting immunotherapy response in ccRCC, as contemporarily reported in 2018 by two independent research groups[31,33].

Smith *et al*[32] identified a signature marking anti-PD-1 responsiveness associated with hERV expression, while a signature for non-responder tumors was negatively associated with hERV expression[31]. They explored the mechanisms by which hERV expression in tumor cells influenced the TIME in RCC, discovering immune stimulation evidence through RIG-I-like signaling of the hERV-induced adaptive immune response through B cell activation. Also, they showed that hERVs mediated the tumor-specific presentation of targetable viral epitopes, possibly adding a trigger to the antitumor response. On the other hand, ERV proteins were already known to be expressed and immunogenic in ccRCC[34-36].

Similarly, Panda *et al*[34] identified 20 potentially immunogenic ERV (πERVs) in ccRCC in TCGA dataset, demonstrating that πERV-high ccRCC tumors had an increased immune infiltration checkpoint pathway upregulation and higher CD8+ T cell fraction in infiltrating immune cells compared to πERV-low ccRCC tumors[33]. Moreover, πERV-high ccRCC tumors were enriched in *BAP1* mutations. As a further step, they demonstrated that the RNA level of specific ERVs (*ERV3-2*) was an excellent predictor of response to immune checkpoint blockade, as statistically significantly higher in tumors from responders compared with tumors from non-responders patients with metastatic ccRCC treated with single-agent PD-1/PD-L1 antibody[33]. This evidence is significant in light of the confirmed poor prognostic significance of πERV-high and πERV-intermediate expression, as verified by the same authors. The validation sample was represented by πERV-high and πERV-intermediate ccRCC patients treated with standard therapy, showing significantly shorter overall survival (OS) than patients with πERV-low tumors [OS, hazard ration (HR) 1.44 (95%CI: 1.06-1.97), $P = 0.02$][33].

These findings suggested ERVs' striking relevance on the immune checkpoint activation in ccRCC, potentially configuring a new biomarker of inflamed tumors, more likely to respond to ICI immunotherapy.

RCC IN PATIENTS WITH CHRONIC VIRAL INFECTIONS: IS THERE ANY CAUSE-OUTCOME RELATIONSHIP?

Chronic viral infections are often subtended by a dysfunctional immune response, possibly conferring a persistently inflamed status to the host, likely dominated by T-cells exhaustion. Several authors have reported the increased incidence of malignancies in patients with chronic viral infections, and some consistent literature also emerged in the field of renal cancer (Table 2)[37-43].

Chronic HCV infection seems to confer a risk for the development of RCC, according to a cohort study of 67063 HCV-tested patients, among whom RCC was diagnosed in 0.6% of HCV-positive *vs* 0.3% of HCV-negative patients. The univariate HR for RCC among HCV patients was 2.20 (95%CI: 1.32-3.67; $P = 0.0025$). In a

Table 2 Studies reporting the relationship between chronic viral infections and the occurrence of renal cell carcinoma

Ref.	Study type	Type of chronic viral infection	Study population	RCC histology	Mean age (yr)	Aim	Main results/conclusions
Gaughan *et al* [43], 2008	Case series	HIV infection	9 HIV-associated RCC[1]	2 papillary, 1 collecting duct, 6 clear cell	48	To describe the risk factors, clinical findings, pathology, and response to therapy in RCC patients infected with HIV	The clinical presentation and behavior of RCC in patients with HIV infection appeared similar to that of the HIV-negative population and that chronic immunosuppression plays a lesser role than age and exposure to risk factors
Gordon *et al* [38], 2010	Retrospective study	HCV infection	67063 HCV-tested patients: 3057 HCV+ and 64006 HCV-	17 RCC HCV+: 8 clear cell, 6 papillary, 2 mixed clear cell/papillary, 1 undifferentiated/other; 117 HCV-: 92 clear cell, 43 papillary, 9 mixed clear cell/papillary, 26 undifferentiated/other	54 in HCV+, 63 in HCV-	To determine whether HCV infection confers an increased risk for developing RCC	RCC was diagnosed in 0.6% (17/3057) of HCV+ and 0.3% (117/64006) of HCV- patients. HCV infection confers a risk for the development of RCC: Overall HR for RCC among HCV patients 1.77 (95% confidence interval, 1.05-2.98; $P = 0.0313$)
Wiwanitkit [42], 2011	Bioinformatics analysis	HCV infection	NA	NA	NA	To assess the cause–outcome relationship between HCV infection and RCC using the bioinformatics network analysis technique	There might be a cause–outcome relationship between HCV infection and RCC *via* NY-REN-54 (the only one common protein)
Gonzalez *et al* [39], 2015	Prospective study	HCV infection	140 RCC and 100 colon cancer patients (control)	NA	56.7 in RCC patients with viremia, 61.8 in aviremic patients	To determine whether chronic HCV is associated with an increased risk of RCC	11/140 RCC and 1/100 colon cancer patients were HCAB+. Of the HCAB+ patients, 9/11 RCC and 0/1 controls had detectable HCV RNA. In the multivariable logistic regression analysis, being HCV RNA positive was a significant risk factor for RCC ($P = 0.043$)
Wijarnpreecha *et al*[40], 2016	Systematic review and meta-analysis	HCV infection	196826 patients from 7 observational studies (4 cohort and 3 case-control studies). Individuals without HCV infection were used as comparators in cohort studies, individuals without RCC as comparators in the cross-sectional and case-control studies	NA	NA[2]	To assess the risk of RCC in patients with HCV infection	Significantly increased risk of RCC in HCC+ with the pooled risk ratio of 1.86 (95%CI: 1.11-3.11)
Ong *et al*[44], 2016	Case series	HIV infection	7 HIV-associated RCC[1]	5 clear cell, 1 papillary, 1 unknown	56	To report presentation, management and outcomes of RCC patients with HIV infection	RCC patients with HIV infection should be offered all treatment options in the same manner as the general population
Tsimafeyeu *et al* [41], 2020	Retrospective study	HCV infection	44 mRCC patients: 22 HCV+, 22 HCV-	Clear cell	62 in mRCC HCV+, 63 in mRCC HCV-	To evaluate Nivolumab efficacy and safety in mRCC patients with or without chronic HCV infection (OS primary endpoint, PFS, ORR and rate of grade 3–4 adverse events secondary endpoints)	HCV-infected patients had significantly longer OS (27.5 *vs* 21.7, $P = 0.005$) and PFS (7.5 *vs* 4.9, $P = 0.013$), no difference in ORR. Grade 3–4 adverse events were observed in 5 (23%) HCV+ patients and in 3 (14%) HCV- patients

[1]Human immunodeficiency virus infection before renal cell carcinoma (RCC) diagnosis.
[2]Mean age not specified, but hepatitis C virus (HCV)+ RCC patients were significantly younger than HCV-RCC patients.
HCV: Hepatitis C virus; RCC: Renal cell carcinoma; mRCC: Metastatic renal cell carcinoma; HR: Hazard ratio; NA: Not available; HCAB: Hepatitis C antibody; RNA: Ribonucleic acid; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; HIV: Human immunodeficiency virus.

multivariate model that included the risk factors age, race, gender, and chronic kidney disease, the overall HR for RCC among HCV patients was 1.77 (95%CI: 1.05-2.98; P = 0.0313)[37].

In another report, RCC patients were shown to have a higher rate of hepatitis C antibody positivity (11/140, 8%) than colon cancer patients (1/100, 1%, P = 0.01), viremic RCC patients were significantly younger than RCC patients who were HCV RNA negative (P = 0.013)[38].

A meta-analysis of seven observational studies including 196826 patients, the risk of RCC in HCV patients was found to increase with a pooled risk ratio (RR) of 1.86 (95%CI: 1.11-3.11). Nevertheless, the association between RCC and HCV was marginally insignificant after a sensitivity analysis limited only to studies with adjusted analysis, with a pooled RR of 1.50 (95%CI: 0.93-2.42)[39].

In HIV infection, AIDS-related immunosuppression could play the leading role in promoting oncogenic events instead of the viral infection itself. The literature simply included RCC in the expanding array of non-AIDS-defining malignancies that develop during HIV infection[42,43].

On the other hand, subtending viral infections could represent the epiphenomenon of a dysfunctional immune status, maybe more likely to benefit from immune checkpoint blockade[44]. In a matched cohort study, data were collected from 174 patients with metastatic ccRCC, chronic HCV infection (case study group), no evidence of other malignancy or cirrhosis, and had received nivolumab as systemic anticancer treatment[39]. HCV-infected patients had significantly longer OS and progression-free survival (PFS). Median OS was 27.5 (95%CI: 25.3–29.7) and 21.7 (20.3–23.1) in study and control groups, respectively (P = 0.005). Median PFS was 7.5 (5.7–9.3) and 4.9 (4–5.8) (P = 0.013). Despite no differences in objective response rate between groups, patients with HCV had significantly more durable responses (P = 0.01). Such findings are undoubtedly suggestive but still largely insufficient to draw a causality relationship between chronic viral infections and immunogenicity.

The report of acute viral infections triggering an anticancer immune response in patients with solid and hematological malignancies is rather than new. From the first observation by William Coley that non-self-agents can trigger antitumor immune reactivity to the recent findings by our research group about influenza infection in advanced cancer patients treated with ICI immunotherapy, the literature emphasizes the role of extrinsic immune stimulation in modulating the immune reactivity and also the efficacy of inhibitory molecules targeting immune checkpoints[45,46]. Even SARS-CoV-2 was reported as able to exert an abscopal antitumor effect in solid tumors: Cases of partial or complete remission during COVID-19 have been reported in

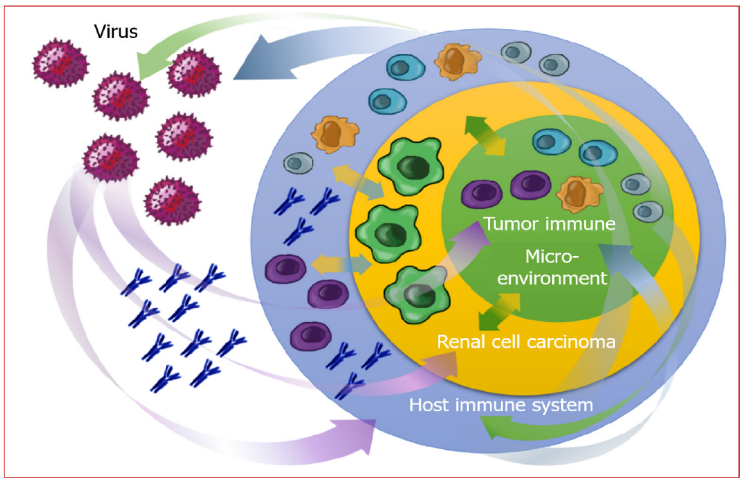

Figure 1 The crosstalk between the virus, the host, and the tumor is likely to influence the mutual interplay between the tumor itself, its immune microenvironment, and the host with renal cell carcinoma.

patients with melanoma and lymphomas without any anticancer treatment, in the latter cases likely due to a direct oncolytic effect on tumor cells[47-49].

Compared to cancer diagnosis in chronically infected individuals, likely driven by immunosuppression and immune exhaustion[50], the occurrence of viral infections in patients with cancer represents an opposite setting. In this case, the encounter with viral antigens could contribute, as a potent exogenous immunological stimulus, to shift the balance between tolerance and activation, likely favorably influencing the TIME and the complex relationships between the tumor and the host (Figure 1).

The possible contribution of viruses in kidney cancers with variant histology

For completeness, state-of-the-art about viruses and kidney cancer also included evidence about collecting duct carcinoma (CDC), rare variant histology with poor prognosis, and challenging therapy[51]. Notably, BKV polyomavirus was reported in the literature as linked to CDC in transplant recipients, again highlighting the role of immunosuppression as the playing field for virus-associated carcinogenesis[52,53].

CONCLUSION

The evidence presented above is a tickling proof-of-concept subtending the possibility to add a dowel for the prediction of cancer patients' outcome to immune checkpoint therapy and even more suggests exploiting the immunogenic potential of viruses for therapeutic purposes in the context of anticancer immunotherapy for RCC. Although manipulating viruses could sound like a dangerous game just in the context of the pandemic currently ongoing, teased by striking findings from this preliminary translational research, the authors of the present opinion review still consider the possibility that dangerous relationships may be the most immunogenic, at least in the context of RCC.

REFERENCES

1 **American Cancer Society**. Viruses that can lead to cancer. [cited 10 March 2021]. Available from: https://www.cancer.org/cancer/cancer-causes/infectious-agents/infections-that-can-lead-to-cancer/viruses.html

2 **Naegele RF**, Granoff A, Darlington RW. The presence of the Lucké herpesvirus genome in induced tadpole tumors and its oncogenicity: Koch-Henle postulates fulfilled. *Proc Natl Acad Sci U S A* 1974; **71**: 830-834 [PMID: 4545010 DOI: 10.1073/pnas.71.3.830]

3 **McKinnell RG**, Cunningham WP. Herpesviruses in metastatic Lucké renal adenocarcinoma. *Differentiation* 1982; **22**: 41-46 [PMID: 6286398 DOI: 10.1111/j.1432-0436.1982.tb01221.x]

4 **McKinnell RG**, Tarin D. Temperature-dependent metastasis of the Lucke renal carcinoma and its significance for studies on mechanisms of metastasis. *Cancer Metastasis Rev* 1984; **3**: 373-386 [PMID: 6097356 DOI: 10.1007/BF00051461]

5 **Motzer R**, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK; CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med* 2021; **384**: 1289-1300 [PMID: 33616314 DOI: 10.1056/NEJMoa2035716]

6 **Choueiri TK**, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, Oyervides Juárez VM, Hsieh JJ, Basso U, Shah AY, Suárez C, Hamzaj A, Goh JC, Barrios C, Richardet M, Porta C, Kowalyszyn R, Feregrino JP, Żołnierek J, Pook D, Kessler ER, Tomita Y, Mizuno R, Bedke J, Zhang J, Maurer MA, Simsek B, Ejzykowicz F, Schwab GM, Apolo AB, Motzer RJ; CheckMate 9ER Investigators. Nivolumab plus Cabozantinib *vs* Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 2021; **384**: 829-841 [PMID: 33657295 DOI: 10.1056/NEJMoa2026982]

7 **Powles T**, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, Nosov D, Pouliot F, Melichar B, Vynnychenko I, Azevedo SJ, Borchiellini D, McDermott RS, Bedke J, Tamada S, Yin L, Chen M, Molife LR, Atkins MB, Rini BI. Pembrolizumab plus axitinib *vs* sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2020; **21**: 1563-1573 [PMID: 33284113 DOI: 10.1016/S1470-2045(20)30436-8]

8 **Motzer RJ**, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab *vs* Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2018; **378**: 1277-1290 [PMID: 29562145 DOI: 10.1056/NEJMoa1712126]

9 **Bersanelli M**, Gnetti L, Varotti E, Ampollini L, Carbognani P, Leonardi F, Rusca M, Campanini N, Ziglioli F, Dadomo CI, Pilato FP, Cortellini A, Rapacchi E, Caruso G, Silini EM, Maestroni U, Buti S. Immune context characterization and heterogeneity in primary tumors and pulmonary metastases from renal cell carcinoma. *Immunotherapy* 2019; **11**: 21-35 [PMID: 30702014 DOI: 10.2217/imt-2018-0097]

10 **Marabelle A**, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K, Bang YJ. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020; **21**: 1353-1365 [PMID: 32919526 DOI: 10.1016/S1470-2045(20)30445-9]

11 **Motzer RJ**, Banchereau R, Hamidi H, Powles T, McDermott D, Atkins MB, Escudier B, Liu LF, Leng N, Abbas AR, Fan J, Koeppen H, Lin J, Carroll S, Hashimoto K, Mariathasan S, Green M, Tayama D, Hegde PS, Schiff C, Huseni MA, Rini B. Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. *Cancer Cell* 2020; **38**: 803-817.e4 [PMID: 33157048 DOI: 10.1016/j.ccell.2020.10.011]

12 **Brugarolas J**, Rajaram S, Christie A, Kapur P. The Evolution of Angiogenic and Inflamed Tumors: The Renal Cancer Paradigm. *Cancer Cell* 2020; **38**: 771-773 [PMID: 33157049 DOI: 10.1016/j.ccell.2020.10.021]

13 **Kaufman HL**, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, Brownell I, Lewis KD, Lorch JH, Chin K, Mahnke L, von Heydebreck A, Cuillerot JM, Nghiem P. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol* 2016; **17**: 1374-1385 [PMID: 27592805 DOI: 10.1016/S1470-2045(16)30364-3]

14 **Samimi M**, Kervarrec T, Touze A. Immunobiology of Merkel cell carcinoma. *Curr Opin Oncol* 2020; **32**: 114-121 [PMID: 31972727 DOI: 10.1097/CCO.0000000000000608]

15 **Mendoza MD**, Santonja C, Gonzalez-Vela C, Concha A, Iglesias Pena N, Andrés-Esteban EM, Vaque JP, Cereceda L, Pajares R, Kutzner H, Requena L, Piris MA. The presence of Merkel cell carcinoma polyomavirus is associated with a distinct phenotype in neoplastic Merkel cell carcinoma cells and their tissue microenvironment. *PLoS One* 2020; **15**: e0232517 [PMID: 32687503 DOI: 10.1371/journal.pone.0232517]

16 **Bulut Y**, Ozdemir E, Ozercan HI, Etem EO, Aker F, Toraman ZA, Seyrek A, Firdolas F. Potential relationship between BK virus and renal cell carcinoma. *J Med Virol* 2013; **85**: 1085-1089 [PMID: 23588736 DOI: 10.1002/jmv.23559]

17 **Neirynck V**, Claes K, Naesens M, De Wever L, Pirenne J, Kuypers D, Vanrenterghem Y, Poppel HV, Kabanda A, Lerut E. Renal cell carcinoma in the allograft: what is the role of polyomavirus? *Case Rep Nephrol Urol* 2012; **2**: 125-134 [PMID: 23197968 DOI: 10.1159/000341917]

18 **Kim KH**, Han EM, Lee ES, Park HS, Kim I, Kim YS. Epstein-Barr virus infection in sarcomatoid renal cell carcinoma tissues. *BJU Int* 2005; **96**: 547-552 [PMID: 16104908 DOI: 10.1111/j.1464-410X.2005.05682.x]

19 **Salehipoor M**, Khezri A, Behzad-Behbahani A, Geramizadeh B, Rahsaz M, Aghdaei M, Afrasiabi MA. Role of viruses in renal cell carcinoma. *Saudi J Kidney Dis Transpl* 2012; **23**: 53-57 [PMID: 22237219]

20 **Farhadi A**, Behzad-Behbahani A, Geramizadeh B, Sekawi Z, Rahsaz M, Sharifzadeh S. High-risk

human papillomavirus infection in different histological subtypes of renal cell carcinoma. *J Med Virol* 2014; **86**: 1134-1144 [PMID: 24700118 DOI: 10.1002/jmv.23945]

21 **Frascà GM**, Sandrini S, Cosmai L, Porta C, Asch W, Santoni M, Salviani C, D'Errico A, Malvi D, Balestra E, Gallieni M. Renal cancer in kidney transplanted patients. *J Nephrol* 2015; **28**: 659-668 [PMID: 26202137 DOI: 10.1007/s40620-015-0219-8]

22 **Moris D**, Kakavia K, Argyrou C, Garmpis N, Bokos J, Vernadakis S, Diles K, Sotirchos G, Boletis J, Zavos G. *De Novo* Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-center Experience. *Anticancer Res* 2017; **37**: 773-779 [PMID: 28179329 DOI: 10.21873/anticanres.11376]

23 **Wang Y**, Lan GB, Peng FH, Xie XB. Cancer risks in recipients of renal transplants: a meta-analysis of cohort studies. *Oncotarget* 2018; **9**: 15375-15385 [PMID: 29632651 DOI: 10.18632/oncotarget.23841]

24 **Gerlinger M**, Horswell S, Larkin J, Rowan AJ, Salm MP, Varela I, Fisher R, McGranahan N, Matthews N, Santos CR, Martinez P, Phillimore B, Begum S, Rabinowitz A, Spencer-Dene B, Gulati S, Bates PA, Stamp G, Pickering L, Gore M, Nicol DL, Hazell S, Futreal PA, Stewart A, Swanton C. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. *Nat Genet* 2014; **46**: 225-233 [PMID: 24487277 DOI: 10.1038/ng.2891]

25 **Debien V**, Thouvenin J, Lindner V, Barthélémy P, Lang H, Flippot R, Malouf GG. Sarcomatoid Dedifferentiation in Renal Cell Carcinoma: From Novel Molecular Insights to New Clinical Opportunities. *Cancers (Basel)* 2019; **12** [PMID: 31906050 DOI: 10.3390/cancers12010099]

26 **Tannir NM**, Signoretti S, Choueiri TK, McDermott DF, Motzer RJ, Flaifel A, Pignon JC, Ficial M, Frontera OA, George S, Powles T, Donskov F, Harrison MR, Barthélémy P, Tykodi SS, Kocsis J, Ravaud A, Rodriguez-Cid JR, Pal SK, Murad AM, Ishii Y, Saggi SS, McHenry MB, Rini BI. Efficacy and Safety of Nivolumab Plus Ipilimumab *vs* Sunitinib in First-line Treatment of Patients with Advanced Sarcomatoid Renal Cell Carcinoma. *Clin Cancer Res* 2021; **27**: 78-86 [PMID: 32873572 DOI: 10.1158/1078-0432.CCR-20-2063]

27 **Banchereau R**, Leng N, Zill O, Sokol E, Liu G, Pavlick D, Maund S, Liu LF, Kadel E 3rd, Baldwin N, Jhunjhunwala S, Nickles D, Assaf ZJ, Bower D, Patil N, McCleland M, Shames D, Molinero L, Huseni M, Sanjabi S, Cummings C, Mellman I, Mariathasan S, Hegde P, Powles T. Molecular determinants of response to PD-L1 blockade across tumor types. *Nat Commun* 2021; **12**: 3969 [PMID: 34172722 DOI: 10.1038/s41467-021-24112-w]

28 **Quhal F**, Mori K, Fajkovic H, Remzi M, Shariat SF, Schmidinger M. Immunotherapy-based combinations in the first-line treatment of metastatic renal cell carcinoma with sarcomatoid features: a systematic review and network meta-analysis. *Curr Opin Urol* 2022; **32**: 61-68 [PMID: 34720102 DOI: 10.1097/MOU.0000000000000940]

29 **Motzer RJ**, Choueiri TK, Powles T, Burotto M, Bourlon MT, Hsieh JJ, Maruzzo M, Shah AY, Suarez C, Barrios CH, Richardet ME, Porta C, Goh JC, Tomita Y, Bedke J, Zhang J, Simsek B, Scheffold C, Gupta S, Apolo AB. Nivolumab + cabozantinib (NIVO+CABO) *vs* sunitinib (SUN) for advanced renal cell carcinoma (aRCC): Outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. *J Clin Oncol* 2021; 39 [DOI: 10.1200/jco.2021.39.6_suppl.308]

30 **Rini BI**, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Soulieres D, Melichar B, Vynnychenko I, Azevedo SJ, Borchiellini D, McDermott RS, Bedke J, Tamada S, Wan S, Perini RF, Chen M, Atkins MB, Powles T. Pembrolizumab (pembro) plus axitinib (axi) *vs* sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. *J Clin Oncol* 2019; **37**: 4500 [DOI: 10.1200/jco.2019.37.15_suppl.4500]

31 **Yin Y**, Zhou L, Yuan S. Enigma of Retrotransposon Biology in Mammalian Early Embryos and Embryonic Stem Cells. *Stem Cells Int* 2018; **2018**: 6239245 [PMID: 30123290 DOI: 10.1155/2018/6239245]

32 **Smith CC**, Beckermann KE, Bortone DS, De Cubas AA, Bixby LM, Lee SJ, Panda A, Ganesan S, Bhanot G, Wallen EM, Milowsky MI, Kim WY, Rathmell WK, Swanstrom R, Parker JS, Serody JS, Selitsky SR, Vincent BG. Endogenous retroviral signatures predict immunotherapy response in clear cell renal cell carcinoma. *J Clin Invest* 2018; **128**: 4804-4820 [PMID: 30137025 DOI: 10.1172/JCI121476]

33 **Siebenthall KT**, Miller CP, Vierstra JD, Mathieu J, Tretiakova M, Reynolds A, Sandstrom R, Rynes E, Haugen E, Johnson A, Nelson J, Bates D, Diegel M, Dunn D, Frerker M, Buckley M, Kaul R, Zheng Y, Himmelfarb J, Ruohola-Baker H, Akilesh S. Integrated epigenomic profiling reveals endogenous retrovirus reactivation in renal cell carcinoma. *EBioMedicine* 2019; **41**: 427-442 [PMID: 30827930 DOI: 10.1016/j.ebiom.2019.01.063]

34 **Panda A**, de Cubas AA, Stein M, Riedlinger G, Kra J, Mayer T, Smith CC, Vincent BG, Serody JS, Beckermann KE, Ganesan S, Bhanot G, Rathmell WK. Endogenous retrovirus expression is associated with response to immune checkpoint blockade in clear cell renal cell carcinoma. *JCI Insight* 2018; **3** [PMID: 30135306 DOI: 10.1172/jci.insight.121522]

35 **Florl AR**, Löwer R, Schmitz-Dräger BJ, Schulz WA. DNA methylation and expression of LINE-1 and HERV-K provirus sequences in urothelial and renal cell carcinomas. *Br J Cancer* 1999; **80**: 1312-1321 [PMID: 10424731 DOI: 10.1038/sj.bjc.6690524]

36 **Cherkasova E**, Scrivani C, Doh S, Weisman Q, Takahashi Y, Harashima N, Yokoyama H, Srinivasan R, Linehan WM, Lerman MI, Childs RW. Detection of an Immunogenic HERV-E Envelope with

Selective Expression in Clear Cell Kidney Cancer. *Cancer Res* 2016; **76**: 2177-2185 [PMID: 26862115 DOI: 10.1158/0008-5472.CAN-15-3139]

37 **Takahashi Y**, Harashima N, Kajigaya S, Yokoyama H, Cherkasova E, McCoy JP, Hanada K, Mena O, Kurlander R, Tawab A, Srinivasan R, Lundqvist A, Malinzak E, Geller N, Lerman MI, Childs RW. Regression of human kidney cancer following allogeneic stem cell transplantation is associated with recognition of an HERV-E antigen by T cells. *J Clin Invest* 2008; **118**: 1099-1109 [PMID: 18292810 DOI: 10.1172/JCI34409]

38 **Gordon SC**, Moonka D, Brown KA, Rogers C, Huang MA, Bhatt N, Lamerato L. Risk for renal cell carcinoma in chronic hepatitis C infection. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1066-1073 [PMID: 20332260 DOI: 10.1158/1055-9965.EPI-09-1275]

39 **Gonzalez HC**, Lamerato L, Rogers CG, Gordon SC. Chronic hepatitis C infection as a risk factor for renal cell carcinoma. *Dig Dis Sci* 2015; **60**: 1820-1824 [PMID: 25592719 DOI: 10.1007/s10620-015-3521-3]

40 **Wijarnpreecha K**, Nissaisorakarn P, Sornprom S, Thongprayoon C, Thamcharoen N, Maneenil K, Podboy AJ, Cheungpasitporn W. Hepatitis C infection and renal cell carcinoma: A systematic review and meta-analysis. *World J Gastrointest Pathophysiol* 2016; **7**: 314-319 [PMID: 27895977 DOI: 10.4291/wjgp.v7.i4.314]

41 **Tsimafeyeu I**, Gafanov R, Protsenko S, Semenova A, Oganesyan A, Nurgaliyev N, Krasny S, Bondarenko A, Safina S, Zakurdaeva K. Nivolumab in patients with metastatic renal cell carcinoma and chronic hepatitis C virus infection. *Cancer Immunol Immunother* 2020; **69**: 983-988 [PMID: 32078017 DOI: 10.1007/s00262-020-02521-y]

42 **Wiwanitkit V**. Renal cell carcinoma and hepatitis C virus infection: is there any cause-outcome relationship? *J Cancer Res Ther* 2011; **7**: 226-227 [PMID: 21768723 DOI: 10.4103/0973-1482.82931]

43 **Gaughan EM**, Dezube BJ, Aboulafia D, Bower M, Stebbing J, Powles T, Pantanowitz L. Human immunodeficiency virus--associated renal cell carcinoma: a transatlantic case series. *Clin Genitourin Cancer* 2008; **6**: 86-90 [PMID: 18824430 DOI: 10.3816/CGC.2008.n.013]

44 **Ong WL**, King K, Koh TL, Chipman M, Royce P, Hoy J, Millar JL. HIV and renal cell carcinoma: Experience in an Australian statewide HIV center. *Asia Pac J Clin Oncol* 2016; **12**: 188-193 [PMID: 26997617 DOI: 10.1111/ajco.12487]

45 **Coley WB**. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. *Clin Orthop Relat Res* 1991; 3-11 [DOI: 10.1097/00000441-189305000-00001]

46 **Bersanelli M**, Scala S, Affanni P, Veronesi L, Colucci ME, Banna GL, Cortellini A, Liotta F. Immunological insights on influenza infection and vaccination during immune checkpoint blockade in cancer patients. *Immunotherapy* 2020; **12**: 105-110 [PMID: 32046555 DOI: 10.2217/imt-2019-0200]

47 **Herrscher H**, Sauer B, Truntzer P, Robert C. Abscopal antitumor effect in a patient with melanoma and coronavirus disease 2019. *Eur J Cancer* 2021; **149**: 91-93 [PMID: 33839589 DOI: 10.1016/j.ejca.2021.03.003]

48 **Challenor S**, Tucker D. SARS-CoV-2-induced remission of Hodgkin lymphoma. *Br J Haematol* 2021; **192**: 415 [PMID: 33386647 DOI: 10.1111/bjh.17116]

49 **Pasin F**, Mascalchi Calveri M, Calabrese A, Pizzarelli G, Bongiovanni I, Andreoli M, Cattaneo C, Rignanese G. Oncolytic effect of SARS-CoV2 in a patient with NK lymphoma. *Acta Biomed* 2020; **91**: ahead of print [PMID: 32921739 DOI: 10.23750/abm.v91i3.10141]

50 **Baniyash M**, Sade-Feldman M, Kanterman J. Chronic inflammation and cancer: suppressing the suppressors. *Cancer Immunol Immunother* 2014; **63**: 11-20 [PMID: 23990173 DOI: 10.1007/s00262-013-1468-9]

51 **Veldhuijzena NMH**, Rookmaakerb MB, van Zuilenb¸AD, Goldschmedingc R, Nguyenc TQ, Boerb WH. BK virus nephropathy, collecting duct cell proliferation and malignancy in a renal allograft: Case history and review of the literature. *Transpl Immunol* 2017; **9**: 33-37 [DOI: 10.1016/j.ehpc.2016.10.003]

52 **Hasan A**, Abozied H, Youssef A, Fayad S, Ismail A. A rare case of collecting duct carcinoma with first presentation of respiratory symptoms. *Urol Case Rep* 2020; **33**: 101367 [PMID: 33102066 DOI: 10.1016/j.eucr.2020.101367]

53 **Dao M**, Pécriaux A, Bessede T, Dürrbach A, Mussini C, Guettier C, Ferlicot S. BK virus-associated collecting duct carcinoma of the renal allograft in a kidney-pancreas allograft recipient. *Oncotarget* 2018; **9**: 15157-15163 [PMID: 29599935 DOI: 10.18632/oncotarget.24552]

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2022 January 25; 11(1): 13-29

DOI: 10.5527/wjn.v11.i1.13

ISSN 2220-6124 (online)

REVIEW

Literature review of the mechanisms of acute kidney injury secondary to acute liver injury

Esther Platt, Enriko Klootwijk, Alan Salama, Brian Davidson, Francis Robertson

ORCID number: Esther Platt 0000-0003-3248-2414; Enriko Klootwijk 0000-0002-7447-4167; Alan Salama 0000-0002-9255-9092; Brian Davidson 0000-0002-9152-5907; Francis Robertson 0000-0001-5016-5944.

Author contributions: Platt E wrote the manuscript which was reviewed and edited by all authors; all authors contributed to the design of the manuscript and reviewed the final manuscript prior to submission.

Conflict-of-interest statement: No author has any conflict of interest to declare.

Country/Territory of origin: United Kingdom

Specialty type: Surgery

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

Open-Access: This article is an open-access article that was

Esther Platt, Brian Davidson, Francis Robertson, Division of Surgery and Interventional Science, University College London, London NW3 2QG, United Kingdom

Enriko Klootwijk, Alan Salama, Department of Renal Medicine, University College London, London NW3 2PF, United Kingdom

Corresponding author: Esther Platt, FRCS (Gen Surg), MA, MBBS, Surgeon, Department of Surgery and Interventional Science, University College London, Royal Free Campus, University College London, No. 9 Floor Royal Free Hospital, Pond Street, London NW3 2QG, United Kingdom. esther.platt.20@ucl.ac.uk

Abstract

People exposed to liver ischaemia reperfusion (IR) injury often develop acute kidney injury and the combination is associated with significant morbidity and mortality. Molecular mediators released by the liver in response to IR injury are the likely cause of acute kidney injury (AKI) in this setting, but the mediators have not yet been identified. Identifying the mechanism of injury will allow the identification of therapeutic targets which may modulate both liver IR injury and AKI following liver IR injury.

Key Words: Liver failure; Liver transplantation; Ischaemia-reperfusion injury; Acute kidney injury; Liver

Core Tip: Acute kidney injury (AKI) following liver injury is likely to be mediated by circulating molecules. Further investigation is required to identify therapeutic targets to modify liver injury and AKI and reduce the morbidity and mortality associated with this condition.

Citation: Platt E, Klootwijk E, Salama A, Davidson B, Robertson F. Literature review of the mechanisms of acute kidney injury secondary to acute liver injury. *World J Nephrol* 2022; 11(1): 13-29

URL: https://www.wjgnet.com/2220-6124/full/v11/i1/13.htm

DOI: https://dx.doi.org/10.5527/wjn.v11.i1.13

Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: May 3, 2021
Revised: May 4, 2021
Accepted: December 25, 2021
Article in press: December 25, 2021
Published online: January 25, 2022

P-Reviewer: Xu XY
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

INTRODUCTION

Ischaemia reperfusion (IR) injury is typified by initial hypoperfusion and inadequate oxygen supply to end organs. This is followed by a secondary inflammatory reperfusion injury which impacts organ function and may affect distant organs[1]. IR injury can occur as part of a global hypoperfusion phenomenon such as that seen in trauma, sepsis and haemorrhage[1-4]. IR injury may also represent a local issue of poor perfusion that primarily affects a single organ or body region.

In the clinical setting, liver IR injury is commonly seen following liver resection and liver transplantation (LT)[5]. Liver IR injury following transplant is associated with major complications related to the liver injury, including early allograft dysfunction, primary nonfunction and ischaemic-type biliary complications[6,7]. In addition to liver specific outcomes, secondary organ injury may occur, which also increases the morbidity and mortality of liver transplantation and resection. Acute kidney injury (AKI) in particular, is very strongly linked to liver IR injury following liver transplantation[8,9]. 40% of liver transplant patients develop AKI, and 7% require renal replacement therapy (RRT)[10]. These patients have an increased mortality with a mortality odds ratio of 2.96, increasing to 8.15 in severe AKI with RRT requirement [10]. AKI post LT is also associated with graft failure, prolonged intensive care unit stay, delay to hospital discharge and subsequent development of chronic kidney disease (CKD)[10-14]. Post-transplant CKD is independently associated with an increase in late mortality and cardiovascular events[11].

Supportive treatment of AKI with renal replacement therapy does not resolve the excess mortality and poor outcomes associated with this condition[15,16]. This may be because AKI needing RRT is a marker of a more global injury affecting the function and viability of multiple organs[15].

There are no specific drug therapies that reverse AKI or block its development. This may in part be related to the overall lack of understanding of the mechanisms underlying the development of AKI following liver IR injury. An improved understanding of the underlying mechanisms of injury is likely to facilitate development of new strategies to avoid and downregulate injury, provide targets for new therapies and improve clinical outcomes post liver transplantation and resection. In the context of liver transplantation, effective therapeutic interventions for both liver IR injury and AKI would also allow expansion of the donor organ pool by inclusion of more marginal grafts, which are more susceptible to IR injury.

In recent years, the indications for liver transplantation have been expanded to include the treatment of primary hepatocellular carcinoma and carefully selected patient groups with some forms of metastatic disease[17,18]. Meeting this potential enormous expansion in transplant demand would necessitate the routine use of marginal grafts. Marginal grafts include those with background hepatic steatosis, grafts from donors following cardiac death and prolonged graft ischaemia times[19, 20]. They are especially susceptible to IR injury and are associated with an increased incidence of AKI and higher mortality[19]. The lack of therapeutic interventions which either provide recipient renal protection from significant liver IR injury or downregulate liver IR injury continues to limit the use of marginal grafts in liver transplantation[21]. Addressing these issues has the potential to revolutionise the use of marginal grafts and meet the current deficit between graft supply and demand.

The clinical importance of both liver IR injury and resultant AKI is clear. Several recent reviews have addressed either mechanisms of liver IR injury or clinical aspects of liver IR injury and AKI. However, no prior review has explored the experimental and clinical evidence for the link between liver IR injury and AKI and the mechanisms mediating AKI after liver transplantation. With a recent expansion in the primary literature on this topic, we believe a review is now warranted to crystalise current understanding, identify unanswered questions and to prioritise future research. In this review we will pull together current evidence for the molecular and physiological mechanisms of kidney injury following liver IR injury.

Figure 1 provides a schematic summary of the evidence for pathways mediating liver IR injury leading to kidney injury that will be discussed throughout this review.

RENAL INJURY IS DIRECTLY LINKED TO LIVER IR INJURY AND OCCURS EARLY FOLLOWING LIVER REPERFUSION

The link between liver IR injury and AKI in liver transplantation has been well established in multiple analyses. A retrospective study of 116 patients undergoing

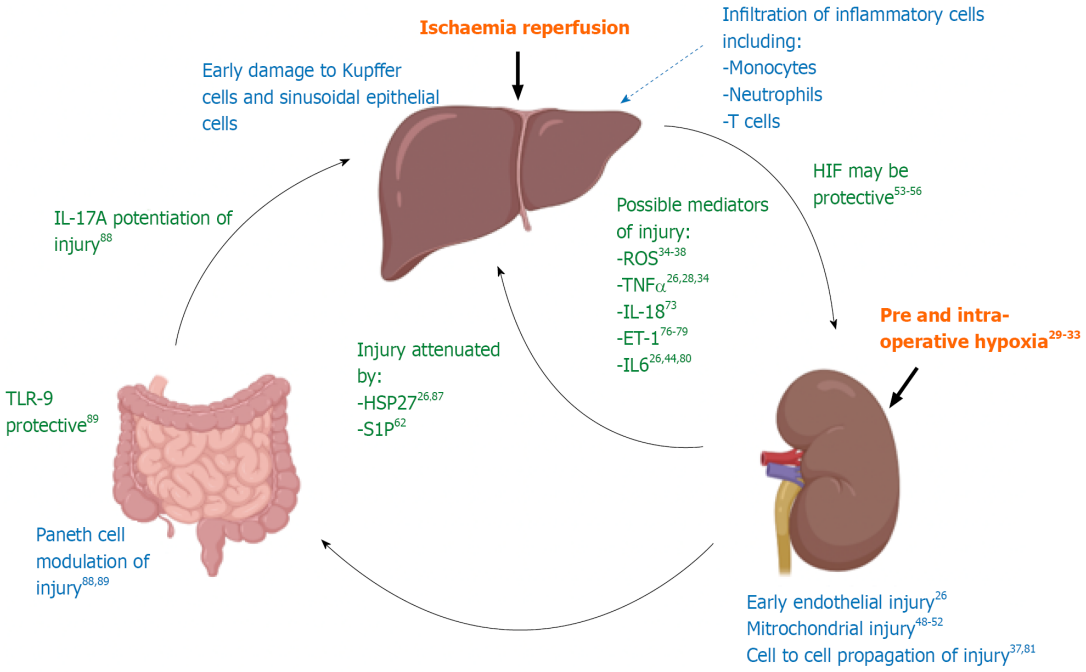

Figure 1 Schematic representation of current evidence to support the mechanistic link between liver IR injury and resultant kidney injury. The evidence for the possible mediators of injury detailed in this diagram will be discussed in more detail in the text of this review. A summary of the major studies discussed in this review can also be found in Supplementary Table 1.

deceased donor liver transplant in our unit identified post transplant serum AST/ALT as the only independent predictor of early post-operative AKI[8], a finding also demonstrated by Jochmans *et al*[9] in their prospective analysis of 88 patients who received livers from donation after brainstem death donors. These clinical data are supported by findings from rodent models of liver IR injury, typified by Lee *et al*[22], who demonstrated a direct relationship between plasma ALT and severity of AKI at 4 h and 24 h in a mouse model of partial hepatic ischaemia (right lobe of liver spared).

Renal injury is not only linked to liver ischaemia injury, but occurs promptly after reperfusion, both in the clinical setting and in animal models. In human liver transplantation, Neutrophil Gelatinase Associated Lipocalin (NGAL), a biomarker of early renal injury, is elevated in urine as early as two hours post reperfusion[23].

In rodent models of liver IR injury, histologically demonstrable renal injury is evident two to four hours post liver reperfusion[24]. Key histological features of renal injury in this context include hyperplasia and necrosis of the juxta-glomerular apparatus, endothelial apoptosis and multifocal acute tubular injury with disruption of F-actin cytoskeletal architecture, leading to S3 segment proximal tubule necrosis, focal tubular simplification (loss of brush border with cellular flattening), cytoplasmic vacuolisation, dilated tubular lumina and focal granular bile/haem casts[22,25,26], as depicted in Figure 2. A standardised grading system for severity of renal injury in rodent models of liver IR injury and AKI, including stratification of histological findings that are more associated with severe AKI, has not yet been developed. Additionally, both the sequence of injury and time frame for improvement in histological changes has not been fully defined.

The development of renal injury within a few hours of liver IR injury in both human clinical and animal experimental data hints at direct transmission of injury from liver to kidney. Liver derived molecules, washed out of the liver during organ reperfusion, may be critical mediators of AKI in this context. As the first cells to encounter haematologically transmitted mediators of injury, endothelial cells might be expected to bear the initial brunt of injury. In rodent models of liver IR injury and AKI, renal endothelial injury predominates[25], supporting this hypothesis. Human histological data is sparse and so we await verification that the rodent pattern of renal injury occurs in the human setting. An *in vitro* human model that permitted demonstration of haematological transmission of liver IR injury to the kidney would also be of huge experimental benefit. This has yet to be developed.

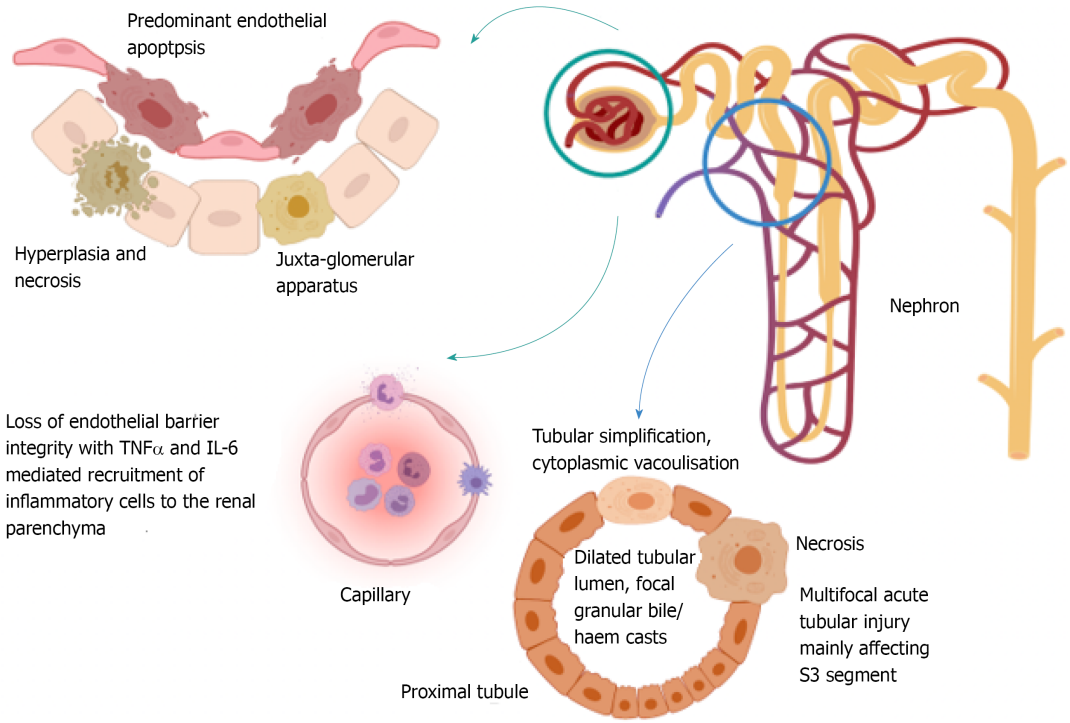

Figure 2 Diagrammatic representation of the current understanding of histological changes within the kidney that accompany acute kidney injury following liver ischaemia reperfusion injury. These data are obtained from animal studies. To date no objective grading system for histological severity of injury has been developed which means that only limited comparison of injury severity between studies is possible. Development of an objective scoring system across the first 48 h of renal injury would be of great benefit in this field of research.

SETTING THE STAGE FOR RENAL INJURY POST LIVER IR INJURY: PRE-OPERATIVE AND INTRA-OPERATIVE PROMOTERS OF INJURY

Whilst molecular mediators released by the liver following IR injury are likely to play a key role in renal injury, evidence suggests that renal injury following liver IR injury is a two-hit phenomenon. Both pre-existing renal abnormalities and intra-operative fluctuations in arterial oxygen concentrations may render the kidney relatively chronically hypoxic and prime it for further damage by circulating mediators of reperfusion injury[27,28]. This seems to be a different phenomenon from controlled ischaemic pre-conditioning which appears to reduce liver and renal injury in a mouse model of liver IR (unpublished data).

Background liver cirrhosis is associated with chronic renal injury and poor renal perfusion which may predispose the kidney to further injury

Renal biopsies performed in the context of cirrhosis demonstrate pathological changes in the kidney, mainly centred around the glomerulus, in 70% of patients. These include mesangial expansion, thickening of capillary walls, a mild increase in the number and size of endothelial and epithelial cells and IgA deposition[28]. These changes may reflect the chronic release of pro-inflammatory mediators from ongoing chronic inflammation in the liver.

Cirrhosis also reduces systemic vascular resistance[28]. When the increased cardiac output can no longer compensate for the reduction in systemic resistance there is arterial hypoperfusion. This leads to activation of vasoconstrictor systems, including the sympathetic nervous system and the renin: Angiotensin: Aldosterone axis with hypersecretion of Anti-Diuretic Hormone. The net result is Na^+ and water retention but with hypovolaemia, renal arterial hypoperfusion and renal vasoconstriction leading to renal failure[28]. This pre-existing inflammatory and hypoxic injury may prime the kidney for further injury during liver transplantation.

There may be intra-operative fluctuations in renal perfusion during liver transplantation leading to a primary kidney insult before liver IR injury

Liver transplantation results in huge fluctuations in mean arterial pressure (MAP) but there is conflicting evidence for an association between MAP and AKI. In a

retrospective study of patients undergoing living donor liver transplantation, severe hypotension (MAP < 40) in the recipient for even less than 10 min was independently related to development of post-operative AKI[29]. In a rat model of liver transplantation with doppler assessment of renal artery flow, Kong *et al*[24] noted increased renal resistive index (RI) during the anhepatic phase and reduced renal RI (compared to background) immediately post reperfusion (although this normalised within 30 min). The findings indicate maldistribution of blood flow to the kidney during the anhepatic phase with increased renal vein pressure secondary to IVC clamping serving to increase renal RI and reduce renal perfusion. Reperfusion is associated with reduced renal arteriolar tone, which the authors suggest may be due to an imbalance between vasoconstrictive and vasodilative factors, disturbing the adaptive capacity of the renal vasculature (not measured in this study). RI did not correlate with the development of AKI at 30 min and 2 h post operatively with this animal model and so RI and renal perfusion may not be the most important factors influencing AKI development.

Kandil *et al*[30] demonstrated similar fluctuations in MAP between the anhepatic and post reperfusion phases of human liver transplantation, although these were not statistically evaluated. In this double-blinded trial, patients were randomised to intra- and post-operative terlipressin infusion or placebo. Terlipressin induces systemic arterial vasoconstriction with renal sparing. It was hypothesised that systemic vascular resistance support with terlipressin would improve renal perfusion and reduce post-operative renal injury. However, the authors demonstrated equivalent incidence of AKI in both the terlipressin and placebo groups which was subsequently supported by evidence from a meta-analysis on the subject[31]. Other causes of fluctuating MAP that may contribute to renal hypoperfusion in addition to systemic vascular resistance were not evaluated in this study.

Thus, whilst a short period of significant hypotension may promote the development of post-operative AKI, the relationship between renal perfusion and subsequent development of AKI requires further investigation and so far evidence suggests that renal perfusion may be less important than circulating factors for the development of AKI following liver IR injury.

Renal hypoxia in liver transplantation may promote development of liver IR induced AKI

In human liver transplantation, low arterial oxygen concentration at 5 min post reperfusion is independently associated with development of AKI (this study included assessment of hypotension)[32]. Arterial hypoxia may result in renal hypoxia, causing primary renal injury. However, only absolute oxygen concentrations rather than relative changes were evaluated in this study. It may be that the relative drop in arterial oxygen concentration at reperfusion reflects the degree of ischaemia and oxygen debt within the donor graft, with higher oxygen tension gradients between the recipient vasculature and more profoundly ischaemic grafts (although this has not yet been evaluated experimentally). Post reperfusion arterial hypoxiaemia may therefore be a surrogate measure of liver IR injury, rather than arterial hypoxia providing a direct contribution to renal injury.

That said, the kidney is highly susceptible to hypoxic injury. Under normal physiological conditions, 80% of the renal oxygen requirement is used to drive the Na^+/K^+/ATPase pump in the proximal tubule. To meet these demands, the kidney is rich in vascular endothelium and has an excellent blood supply[27]. This in turn may make the kidney particularly vulnerable to circulating cytokines which trigger endothelial injury, especially in the situation of mass dilation of capillary beds as can occur during reperfusion secondary to the imbalance of vasodilatory and vasoconstrictive factors discussed in section 1[24].

Put together, the data suggest that the kidney is vulnerable to hypoxic injury and that post reperfusion arterial hypoxia is linked to the severity of renal injury following liver IR injury. Clinically it would be difficult to tease out the relative contributions to AKI from primary renal hypoxia and the more severe liver IR injury that is suggested by arterial hypoxia. Use of in vitro human models of injury where renal hypoxia can be controlled independently of liver IR injury would help to resolve this question. Such models have not yet been reported in the literature.

WHAT ARE THE MOLECULAR MEDIATORS OF RENAL INJURY FOLLOWING LIVER IR INJURY?

Many inflammatory mediators have been implicated in liver IR injury and/or resultant AKI. The discussion below will focus on the major molecules (both injurious and protective) of current investigative interest and draw together the discussion in the literature to provide an overview of current understanding.

Reactive oxygen species may be critical in the early transmission of injury to the kidney following liver IR injury

Reactive oxygen species may originate from the liver and circulate to the kidney[33] or arise primarily in the kidney, where they may be generated following endothelial injury and poor capillary perfusion with resultant relative hypoxia. Hydrogen peroxide (H_2O_2), superoxide anion and hydroxyl radical have all been implicated in this process[34]. Oxidative stress is thought to be the main mediator of primary tissue damage during the first four hours of reperfusion. In a rat model of liver transplantation, oxidative stress in the kidney was shown to increase roughly 2.5 fold and peak at 8 h post reperfusion (measured as H_2O_2 normalised to sham laparotomy) [35,36]. Reactive oxygen species (ROS) bind to critical cellular biomolecules including proteins, DNA and membrane lipids, and cause oxidative modification, with resultant tissue injury[37].

The detrimental action of ROS may be potentiated by ongoing release of ROS from infiltrating inflammatory cells in the later phase of liver reperfusion injury. Activated neutrophils and macrophages release ROS, including superoxide anions and hydroxyl radicals which promote cell death[33]. However, in the longer term ROS may also be regenerative; late neutrophil release of ROS may play a key role in the development of reparative macrophages to orchestrate liver tissue repair following liver injury[38].

Albumin, which acts as a free radical scavenger and endothelium stabiliser is protective in this clinical context; low circulating levels of albumin as found in advanced liver disease are associated with an increased incidence of AKI post liver transplantation[39]. Likewise, administration of various antioxidants and free radical scavengers have been shown to reduce markers of renal oxidative stress and attenuate injury post liver IR in different animal models[40,41]. Iron free radicals may play an important role in the generation of ROS and ferroptosis[42]. Desferrioxamine (DFO), the iron chelator, blocks oxygen free radical production and lipid peroxidation. Administration of DFO was found to attenuate liver IR injury in pigs and was associated with no or subtle tubular injury. Pigs exposed to liver IR injury without DFO demonstrated extensive necrosis of tubular epithelial cells and dilatation of tubular lumina, indicating severe renal injury[43]. Notably the circulating serum iron concentration was not different between DFO-treated animals and controls, implying a specific function of DFO with reactive iron species. It is not known whether this function is separate from the iron binding capacity of DFO.

These findings have not been successfully translated to the clinical setting. Administration of N-acetylcysteine during major liver surgery, including transplantation, is associated with a modest improvement in transaminase levels without impacting either AKI, graft or patient survival[44-46]. Thus whilst ROS are likely to be critical in the early mediation of AKI following liver IR injury, further work is required to identify clinically useful targets that will downregulate injury following liver transplantation and hepatic resection.

Mitochondria are vulnerable to injury and may be the main site of ROS production following liver IR injury

Mitochondria are believed to play a key role in the pathogenesis of renal injury following a variety of insults, with reduced biogenesis (generation of new mitochondria in response to increased energy demand, mitochondrial stress or damage) resulting in attenuated capacity to meet the energy demand and ATP production necessary for injured cells. Mitochondria are also the key site of ROS generation within the cell[35] and ironically mitochondrial injury may also be mediated by ROS[47] or iron species, with DFO demonstrated to attenuate mitochondrial injury in other settings[48]. In a rat model of liver transplantation and AKI, Liu *et al*[49] demonstrated a reduction in key proteins (and mRNA) involved in or regulating mitochondrial biogenesis, fission and fusion including AS-B, ND3, PGC-1α, Tfam, Drp-1 and Fis-1. Mediators of mitophagy and autophagy (PINK-1 and LC3) were also upregulated with AKI in this model. Stimulation of mitochondrial

biogenesis has also been demonstrated to reduce renal IR injury[50,51].

Taken together, the data on ROS suggest local involvement in the pathogenesis of both liver IR injury and subsequent renal injury, with mitochondrial involvement in both the generation of ROS and mediation of ROS effects. However, demonstration of direct haematological transmission of ROS from liver to kidney producing subsequent kidney injury has not been demonstrated.

Hypoxia Inducible Factors may be protective following liver IR injury

Hypoxia inducible factor 1 (HIF-1) is an important mediator of the cellular transcriptional response to hypoxia and plays a key role in the response to liver IR injury. HIF-1 comprises an oxygen destructible alpha subunit and an oxygen-indestructible beta subunit, which dimerise under hypoxic conditions.

HIF-1α silencing pre-injury promotes cellular damage in response to hypoxia, leading to increased serum levels of glucose, lipids, ALT and AST[52]. Conversely, pre-injury activation of HIF-1α attenuates hepatic IR injury by attenuating liver necrosis, the inflammatory response, oxidative stress and apoptosis[53]. HIF-1α stability is partially mediated by the oxygen sensing prolyl hydroxylase domain 1 (PHD1), which under normoxic conditions tags HIF-1α for proteosomal degradation. Interestingly PHD1 function is repressed by miR122, a target gene of HIF-1α, which is almost exclusively expressed in hepatocytes[54]. By this mechanism, HIF-1α enhances HIF mediated cellular responses through PHD1 repression.

Downstream actions of HIF-1 may be key in the attenuation of liver IR injury with subsequent downregulation of AKI but the exact involvement and mechanisms remain unclear. It may be that such effects are mediated by other microRNAs involved in the transcriptional response to HIF-1[54]. The concentration of microRNAs from donor liver perfusate (but not tissue) at the end of cold ischaemia has been linked to elevated AST and graft long term survival[56]. If present in perfusate, these microRNAs may be produced by damaged liver cells that are being flushed out of the liver. The role of such microRNAs in the mediation of kidney injury requires further investigation.

CYTOKINES

Cytokines released from the liver following IR injury

A multitude of cytokines are upregulated in response to liver IR injury. Bezinover *et al*[57] evaluated cytokine upregulation in response to the ischaemia and reperfusion phases of human liver IR injury in 11 extended criteria donor grafts and 6 standard criteria donor grafts for liver transplantation. They obtained samples from the portal vein (prior to reperfusion, thought to represent the ischaemic phase of IR injury), the hepatic veins (at the beginning and end of post implantation liver flush with recipient circulating blood, thought to represent the reperfusion phase of IR injury) and arterial samples (from recipient prior to reperfusion and at 10 min and 20 min post reperfusion). Samples were analysed for TNF, IL-1, IL-2, IL-6 and IL-8 with comparison between levels of individual cytokines at each location. The results suggest early hepatic release of IL-6 during the ischaemic phase. This is followed by TNFα release (without observed increase in systemic circulating TNFα). IL-2 was likewise released from the liver towards the end of reperfusion. IL-1 was released from the liver during the process of reperfusion, without elevated levels seen in systemic samples. IL-8 and TNF are both known to be released by various cells including activated Kupffer cells in response to IR injury[58,59]. IL-8 is chemotactic, leading to recruitment of neutrophils to injured tissues[59], whilst TNFα is important for cell signalling leading to apoptosis or necrosis and neutrophil recruitment[60]. Interestingly, no difference was noted in IL-8 and TNFα release from standard and extended criteria groups. This is significant; given that extended criteria grafts are strongly associated with IR injury[21], higher concentrations of IL-8 and TNFα would be expected from this cohort. Thus release of IL-8 and TNFα may be associated with, but potentially not mechanistic to, IR injury and AKI development.

To summarise, in contrast to most published studies which focus on animal models, Bezinover *et al*[57] attempted to provide real-time human data on liver IR injury and hinted at possible temporal relationships between different cytokines in this context including IL-6, TNFα, IL-2 and IL-1. However, the study made significant assumptions, with no independent experimental validation of their methodology which matched sampling from different liver sites to the various phases of IR injury (for example portal vein sampling was matched to pre-reperfusion phase of injury). Such assumptions may explain the lack of expected difference in cytokine levels

between standard and extended criteria grafts. Additionally, the short period of reperfusion may explain the lack of correlation between liver flush samples and systemic samples. The "reperfusion phase" was only 20 min and therefore further changes within the liver during reperfusion injury may well have been missed in this data. Data from systemic blood samples over a longer time phase would have been interesting in this context.

A pilot study evaluating pre-conditioning in human liver transplantation performed in our unit investigated circulating cytokines at two hours post reperfusion. Levels of IL-6, IL-8, IL-10 and IL-17α were all significantly elevated, whilst plasma levels of IL-2, IFNγ and TNFα did not change during the peri-transplant period[61]. In addition, IL-10 was particularly associated with marginal grafts in this study, although small patient numbers mean that these data are not conclusive.

In a mouse model of 90 min partial hepatic IR injury (right lobe spared), Lee *et al*[62] demonstrated elevated serum IL-6, TNFα and MCP-1 at 6 h. These findings tallied with those from a previous study by the same authors that identified hepatic mRNA upregulation of TNFα, Intracellular Adhesion Molecule 1 (ICAM-1), Keratinocyte-derived Chemokine (KC), Monocyte Chemoattractant protein-1 (MCP-1) and Macrophage Inflammatory Protein-2 (MIP-2) following 60 min partial liver ischaemia [22]. This pattern of upregulation and protein expression is supported by other animal studies of hepatic IR injury[26].

In summary, investigation of liver cytokine release following IR injury has identified numerous molecules that may be present in serum and are capable of transmitting injury to the kidney. However, results between studies are conflicting and there is no clear evidence that the cytokines are responsible for AKI in this context. Further clinical studies that make use of targeted cytokine inhibition or specific rodent knockout models are required to link individual cytokines with AKI. Clarifying liver origin of the cytokine would also be important in establishing the pathway of injury. Additionally, single cell analysis of key liver cells in response to injury might help to identify new mediators of injury that have not been investigated to date.

Cytokines are primarily released from non-parenchymal cells in early liver IR injury

Non parenchymal cells (*i.e.*, non-hepatocytes) seem to be key in the mediation of early liver IR injury[63]. Sinusoidal endothelial cells are damaged during ischaemia, whilst Kupffer cells appear to be activated in response to reperfusion injury, demonstrating five times the TNFα production of control animals[64] in addition to IL-1 and superoxide anions[63]. TNFα production in Kupffer cells may be primarily driven by ROS[65]. In a rat model of liver transplantation, ischaemia-reperfusion preconditioned livers demonstrated a reduction in Kupffer cell superoxide formation, reduced TNF production and reduced non-parenchymal cell death leading to improved recipient survival[66], again suggesting that Kupffer cells are key in the mediation of injury. Acute liver graft failure has been linked to loss of viability of sinusoidal cells and activation of Kupffer cells, further demonstrating the importance of these cell types in the mediation of IR injury[64].

The late phase of liver reperfusion injury is categorised by infiltration of neutrophils, T lymphocytes and monocytes[67-69]. These cells are recruited to the liver parenchyma by upregulation of ICAM-1, VCAM-1 and MCP-1 on damaged hepatocytes and SECs. The infiltrating cells secrete matrix metalloproteinases, other proteases and ROS which cause further liver damage[68,70].

In summary, activation of non-parenchymal cells in the liver is fundamental for the early stages of IR injury. Inflammatory cells are recruited to the liver parenchyma by damaged hepatocytes and SECs and drive ongoing inflammation. Single cell analysis of non-parenchymal cells following liver IR injury may identify key transmitters of renal injury and clarify existing data.

The key cytokine culprits implicated in the mediation of renal injury

Many cytokines have been proposed as mediators of kidney injury following hepatic IR injury. Pulitano *et al*[71] performed molecular profiling of liver biopsies in 65 patients undergoing full size liver graft transplantation. Wedge biopsies were taken from the liver following graft preservation and 90 min after reperfusion in addition to serum samples preoperatively, 30 min after liver reperfusion and on post-operative days 1, 2, 5 and 7. 32% of recipients developed AKI. The authors demonstrated mRNA upregulation in 23 vasoactive, inflammatory, adhesion molecule, apoptosis inducing and oxidation genes (including ET-1, TNFα, IL-6, IL-18 and ICAM-1). Upregulation of the gene was correlated with serum expression of the protein for ET-1, TNFα, IL-6, IL-18 and RANTES 30 min post liver reperfusion and on post-operative days 1, 2, 5 and 7. Of the studied cytokines, only serum levels of Endothelin-1 (ET-1) and IL-18 were

independently associated with AKI development at post-operative day 1, suggesting a key role for ET-1 and IL-18 in the mediation of injury. Interestingly serum ET-1 also correlated with use of inotropes in donors and hepatic steatosis, both risk factors for liver IR injury, and so alternatively, ET-1 may be a surrogate marker for renal injury (which is related to severity of liver IR injury). Renal biopsies to evaluate local gene expression were not performed in this study and so the relationship between gene induction in the liver and effector genes for injury in the kidney cannot be established. Additionally, this study provides a limited look at 23 known mediators of inflammatory injury. Single cell analysis in this context would provide a more precise look at gene upregulation and potentially provide new targets for investigation.

At best, Pulitano *et al*[71] provides evidence for associations between liver mRNA upregulation, circulating IL-18 and ET-1 and kidney injury. However, causality is not established by these data and alternative explanations exist for the findings.

IL-18 may potentiate renal injury following liver IR injury with IL-18BP providing a protective effect

The IL-18-precursor is constitutively present in nearly all cells, where its activity is balanced by the high affinity IL-18 binding protein (IL-18BP). In its active form IL-18 is mostly secreted by macrophages, including Kupffer cells, although some disease processes lead to an imbalance of IL-18/IL-18BP with the liberation of free IL18 from other cell types. IL-18 is known to be an inducer of inflammatory cytokines[72]. Gonul *et al*[33] investigated the role of IL18 in renal injury post liver IR injury using a rat model of hepatic IR (clamping of portal triad for 1 hour followed by 4 h reperfusion) with administration of intraperitoneal IL-18BP 30 min before commencing the laparotomy for liver IR injury. There was no difference in liver IR injury (as measured by AST/ALT/LDH and histological damage) between the groups, but an almost 50% reduction in serum creatinine with administration of IL-18BP compared to controls. This was confirmed by a significant improvement in histological renal injury with a reduction in mononuclear cell infiltration, glomerular necrosis and tubular epithelial necrosis suggesting that IL-18BP does not modify the primary liver IR injury but is involved in the pathway for secondary renal injury. Findings in this study contrasted to a previous study by the same authors which demonstrated improvement in both liver-IR and renal injury with peritoneal administration of IL-18BP[72]. The authors attribute this difference to the higher dose of IL-18BP used in the first study (100μg versus 50μg in this study). This explanation is in keeping with an overall hypothesis of high IL-18 release in response to liver injury and subsequent haematological washout impacting secondary organs. Of note, both studies used human IL-18BP, which has limited homology with rat IL-18BP. This represents a fundamental flaw, and the studies would be better repeated with rat IL-18BP.

Overall IL-18 may be critical in the mediation of renal injury following liver IR injury. However, these data require validation with rat IL-18BP in the animal model, and successful translation of findings to the human setting.

ET-1 may contribute to renal injury post liver IR injury

In addition to the evidence regarding ET-1 provided above, circulating ET-1 has been demonstrated to correlate with both early reduction in GFR and long-term renal dysfunction in patients with normal renal function who are undergoing first Orthotopic Liver Transplantation (OLT)[74]. Patients with liver disease have background high circulating ET-1, due to increased synthesis and reduced clearance [75]. ET-1 is also significantly elevated at the end of the anhepatic phase of liver transplantation in clinical studies[76], although it may be cleared within 30 min by a functioning liver graft. The significance of this is unclear. ET-1 may contribute to renal injury or be a surrogate marker for MELD score and severity of liver disease, which is independently associated with worse outcomes post liver transplantation[77].

ET-1 has been demonstrated to promote Na^+ retention and increase renal vascular resistance without a significant change in blood pressure in healthy volunteers[78]. This function of ET-1 appears contradictory to evidence presented earlier where a reduction in renal resistive index was seen with reperfusion[24] and may reflect differences between the rat model and human situation or differences between the healthy liver and background liver disease or a compensatory mechanism in response to chronically high ET-1. Additionally, evidence suggests that the oxidative status of the renal microvasculature can significantly influence renal microcirculatory responses to ET-1 which may account for different results in different experimental settings. The vasoactive functions of ET-1 in the kidney may be mediated by its action to increase superoxide accumulation in preglomerular smooth muscle cells. Apocynin (an

NADPH oxidase inhibitor) has been demonstrated to attenuate ET-1's ability to reduce renal blood flow[79].

Cytokines recruit inflammatory cells to the kidney with potentiation of injury

In addition to the role they play in the mediation of liver IR injury, IL-6 and TNFα are upregulated in the kidney in response to liver IR injury. TNFα triggers leukocyte-endothelium interactions and microcirculatory dysfunction and is known to impact renal microvascular oxygen distribution and promote organ damage[27]. It has also been demonstrated to promote migration of inflammatory cells into the renal parenchyma through upregulation of KC (rodent equivalent of IL-8), MCP-1 and MIP-2, with macrophage recruitment[25,33]. This is similar to the functions of TNFα seen in the liver following IR as in section "*Cytokines released from the liver following IR injury*".

Likewise, IL-6 is a major pro-inflammatory cytokine that stimulates release of neutrophils from bone marrow, prevents neutrophil apoptosis and activates neutrophils to produce toxic enzymes. Additionally, IL-6 activates endothelial cells to express adhesion molecules and produce chemokines[43] which promote the recruitment of inflammatory cells to the renal parenchyma. Activated neutrophils release oxygen free radicals, neutrophil elastase and products of arachidonic acid metabolism, further potentiating renal injury[25,80].

Thus both IL-6 and TNFα are believed to be key for the potentiation of renal injury following liver IR injury by recruitment of inflammatory cells as part of the systemic inflammatory response to injury. Further investigation is required to establish other potentiators of injury in this context.

POTENTIATION OF INJURY WITHIN THE KIDNEY: THERE IS CELL TO CELL SIGNALLING OF DAMAGE

There is growing evidence for transmission of injury between cells in a variety of settings. Connexins are a big family of transmembrane proteins, expressed in all human organs and tissues, which form internal gap junctions between cells and manipulate small molecule (less than 1KDa), direct-transfer signalling[36]. Luo specifically investigated the role of Connexin-32 (Cx32), because this connexin is normally richly expressed in the kidney. Cx32 expression was found to increase following reperfusion in a rat model of liver transplantation, peaking in tandem with kidney damage and functional impairment at 8 h[36]. Treatment with 2-APB, a relatively specific inhibitor of Cx32 channels, reduced renal injury. This study only evaluated renal function and would have benefited from measurement of liver injury, both in response to IR and following addition of 2-ARB, to evaluate the specificity of the renal response.

Cx32 expression has been demonstrated to positively correlate to the degree of IR injury in liver biopsies from patients undergoing liver transplantation[81], but human evidence to support the role of Cx32 in subsequent kidney cell to cell transmission of injury is lacking. Such data is worth pursuing, along with supplementary evidence to further define cell to cell signalling in the kidney.

THE INJURED KIDNEY MAY MODULATE THE PROGRESSION OF LIVER IR INJURY

Accumulating evidence suggests that in addition to liver IR injury mediation of renal injury, the kidney itself plays a key role in the potentiation or amelioration of liver injury.

There is demonstrable liver injury after ischaemic renal injury, with derangement of AST/ALT and evidence of hepatocyte apoptosis (*via* activation of NFB-receptor)[82,83]. IL-10, IL-6 and TNFα are upregulated within the liver and multiple markers of oxidative stress have been identified following ischaemic AKI. It is not known whether this is related to systemic inflammation or targeted liver injury. Either way, the effect may be persistent; renal IR injury is associated with the development of hepatic steatosis in the longer term[80].

Human Heat Shock Protein 27 (HSP27) is a member of the chaperone protein family. These proteins are upregulated in response to a variety of cellular stresses. HSP27 is a key stabiliser of F-actin and a potent anti-apoptotic. In a genetically manipulated mouse model with demonstrated robust and widespread overexpression

of HSP27, Park *et al*[25] demonstrated attenuation of both partial liver IR injury (left and middle liver lobe inflow clamped), and secondary renal injury. The hepatic protection was primarily mediated by the kidneys as the liver injury was abolished by unilateral and bilateral nephrectomy. The findings of this study contrast with a previous study by the same group, where HSP27 overexpression provided primary protection against liver IR injury (significantly less necrosis and apoptosis at 2 h post reperfusion)[84]. In that study the HSP27 protection was thought to be mediated by Kupffer cells; depletion of Kupffer cells obliterated protection in HSP27 over-expressing mice but did not impact IR injury in wild type mice. Such results are not in keeping with the previously discussed, known roles of Kupffer cells in liver IR injury. One would expect obliteration of Kupffer cells in wild type mice to downregulate IR injury. Further investigation of these controversies is required but these studies hint that it might be possible to "switch off" liver IR injury and AKI, given the right therapeutic targets.

The sphingosine-1-phosphate (S1P)/$S1P_1$-receptor interaction on endothelial cells is known to be critical in the maintenance of endothelial barrier integrity in the kidney. In a mouse model of hepatic IR injury, pre-treatment with S1P did not significantly attenuate liver injury (ALT/histology) at 6 h but provided marked attenuation at 24 h [62]. Renal injury was reduced at 6 h (TUNEL assay), with significantly improved endothelial integrity and reduced expression of $CD44^+$ cells (indicating a reduction in endothelial injury) compared to non S1P treated mice. Pre-treatment with the $S1P_1$ antagonist, VPC 23019, partially reversed the protection afforded by S1P.

Together these studies support the hypothesis that renal injury is both triggered by early liver IR injury and modulates ongoing liver IR injury. The mechanisms by which this occurs remain unknown but may involve the systemic inflammatory response to renal injury. Further work is required to determine the "switches" that decide whether renal modulation is pro- or anti-inflammatory and to harness these for therapeutic intervention.

THERE MAY BE ADDITIONAL EXTRA-RENAL MODIFICATION OF LIVER IR AND RENAL INJURY

Some recent studies have focussed on the role of the intestinal immune system in primary renal injury leading to secondary liver injury. IL-17A released by Paneth cell degranulation in the small intestine in response to primary renal IR injury contributes to hepatic, renal and intestinal injury, with improvement in all three when IL-17A is depleted[85]. Contrastingly Paneth cell TLR-9 knockout mice demonstrate progression of hepatic, intestinal and renal injury in response to kidney IR injury[86]. These data are obtained from models of kidney IR injury and therefore do not directly relate to liver IR injury. However, future studies to investigate the role of Paneth cells in the mediation of renal and liver injury following IR insult to the liver may reveal similar intriguing findings and provide additional opportunities to modulate the potentiation of systemic and local response to injury.

LIMITATIONS OF THE CURRENT LITERATURE

The studies discussed within this review present some interesting data related to the mechanisms of renal injury secondary to liver IR injury. However, a clear understanding of the pathways mediating the transmission of injury from liver to kidney and back again is not yet within our grasp. Investigative work in this field has relied heavily upon small rodent models. Rodent models often lack applicability to the human setting and clinical interventions that show promise in rodents often fail upon translation to the human setting[44,61,87]. Rodent populations used for experimental work are inbred animals with relatively limited genetic diversity and so cannot fully represent human populations with polymorphic genetic backgrounds[88]. Liver injury often occurs in patients who do not have background "normal" liver (including transplantation, ALF and ACLF). Background altered liver function may prime the immune and/or renal systems to injury, potentiating the effects of an acute insult. This is not accounted for in rodent models and may also impact the applicability of any results to the human setting.

A second limitation with all studies in this field is the difficulty associated with defining AKI clinically. Most studies included here rely upon serum creatinine (+/-

urea), with clinical studies applying the AKIN or KDIGO criteria. Both AKIN and KDIGO rely upon changes in serum creatinine or urine output. Serum creatinine is well known to be a relatively insensitive marker of renal injury. Patients with end-stage liver disease are often deplete in skeletal muscle and so have low circulating creatinine, which may mask underlying renal injury[89,90]. Changes in serum creatinine take time to reflect renal injury, often between 12 and 24 h. During this time, renal injury may be potentiated, with worse long-term outcomes.

A third limitation with studies in this field is the lack of an animal model that allows serial sampling to dynamically assess changes over time. Rodent models are too small to accommodate serial liver and kidney biopsies or blood samples. As demonstrated herein, renal injury and liver injury following liver IR is a dynamic and evolving process. Serial, *in vivo* sampling would be highly informative.

FUTURE DIRECTIONS

Whilst the limitations of rodent models may be here to stay, improved diagnostic methodology for acute kidney injury may be provided by one, or a combination of biomarkers. NGAL shows great promise in this respect[91], and is already being used as an alternative to serum creatinine for the diagnosis of renal injury in some studies. In a study of liver transplant patients, we found that urinary NGAL measured at the time of abdominal closure accurately predicted post-operative AKI[23]. This has been confirmed by other studies[92,93]. The site of release and role of NGAL in liver IR injury leading to renal injury is not currently known. NGAL has multiple functions[94] including iron transport[95]. Speculatively, NGAL could "mop up" iron free radicals which contribute to injury in the context of liver IR and resultant renal injury. An interesting recent study identified that NGAL is co-localised with Arl13b to the primary cilium of human renal tubular epithelial cells in chronic allograft nephropathy [96]. KIM-1, another potential biomarker for renal injury[97] is also expressed on primary cilia[98]. The primary cilium is a key organelle and performs a variety of functions including mechano- and chemo-sensitisation[99]. In liver IR injury, primary cilia are shed into the urine and are demonstrable as early as 1 h post injury[98]. Whether NGAL is co-incidentally shed with cilia, or promotes shedding of cilia, awaits clarification.

CONCLUSION

The mechanisms by which liver injury mediates renal injury require further clarification but it is likely that multiple circulating molecules are involved, including currently unidentified molecules. The kidney may be primed to injury by alterations in renal microcirculation with early endothelial and subsequent tubular injury. Renal injury in turn, may potentiate liver IR injury and this process may involve other organs with immune function, including the gut.

REFERENCES

1 **Wu MY**, Yiang GT, Liao WT, Tsai AP, Cheng YL, Cheng PW, Li CY, Li CJ. Current Mechanistic Concepts in Ischemia and Reperfusion Injury. *Cell Physiol Biochem* 2018; **46**: 1650-1667 [PMID: 29694958 DOI: 10.1159/000489241]

2 **Adembri C**, de Gaudio AR, Novelli GP. Ischaemia-Reperfusion in Sepsis. In: Sepsis and Organ Dysfunction. 2000 [DOI: 10.1007/978-88-470-2284-3_5]

3 **Dorweiler B**, Pruefer D, Andrasi TB, Maksan SM, Schmiedt W, Neufang A, Vahl CF. Ischemia-Reperfusion Injury : Pathophysiology and Clinical Implications. *Eur J Trauma Emerg Surg* 2007; **33**: 600-612 [PMID: 26815087 DOI: 10.1007/s00068-007-7152-z]

4 **Bar-Or D**, Carrick MM, Mains CW, Rael LT, Slone D, Brody EN. Sepsis, oxidative stress, and hypoxia: Are there clues to better treatment? *Redox Rep* 2015; **20**: 193-197 [PMID: 25803628 DOI: 10.1179/1351000215Y.0000000005]

5 **Weigand K**, Brost S, Steinebrunner N, Büchler M, Schemmer P, Müller M. Ischemia/Reperfusion injury in liver surgery and transplantation: pathophysiology. *HPB Surg* 2012; **2012**: 176723 [PMID: 22693364 DOI: 10.1155/2012/176723]

6 **Ito T**, Naini BV, Markovic D, Aziz A, Younan S, Lu M, Hirao H, Kadono K, Kojima H, DiNorcia J 3rd, Agopian VG, Yersiz H, Farmer DG, Busuttil RW, Kupiec-Weglinski JW, Kaldas FM. Ischemia-reperfusion injury and its relationship with early allograft dysfunction in liver transplant patients. *Am*

J Transplant 2021; **21**: 614-625 [PMID: 32713098 DOI: 10.1111/ajt.16219]
7 **Gazia C**, Lenci I, Manzia TM, Martina M, Tisone G, Angelico R, Abenavoli L, Grassi G, Signorello A, Baiocchi L. Current Strategies to Minimize Ischemia-Reperfusion Injury in Liver Transplantation: A Systematic Review. *Rev Recent Clin Trials* 2021 [PMID: 34376136 DOI: 10.2174/1574887116666210729112932]
8 **Rahman S**, Davidson BR, Mallett SV. Early acute kidney injury after liver transplantation: Predisposing factors and clinical implications. *World J Hepatol* 2017; **9**: 823-832 [PMID: 28706581 DOI: 10.4254/wjh.v9.i18.823]
9 **Jochmans I**, Meurisse N, Neyrinck A, Verhaegen M, Monbaliu D, Pirenne J. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: Prospective cohort study. *Liver Transpl* 2017; **23**: 634-644 [PMID: 28124458 DOI: 10.1002/lt.24728]
10 **Thongprayoon C**, Kaewput W, Thamcharoen N, Bathini T, Watthanasuntorn K, Lertjitbanjong P, Sharma K, Salim SA, Ungprasert P, Wijarnpreecha K, Kröner PT, Aeddula NR, Mao MA, Cheungpasitporn W. Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis. *J Clin Med* 2019; **8** [PMID: 30884912 DOI: 10.3390/jcm8030372]
11 **Durand F**, Francoz C, Asrani SK, Khemichian S, Pham TA, Sung RS, Genyk YS, Nadim MK. Acute Kidney Injury After Liver Transplantation. *Transplantation* 2018; **102**: 1636-1649 [PMID: 29847502 DOI: 10.1097/TP.0000000000002305]
12 **Moore JK**, Love E, Craig DG, Hayes PC, Simpson KJ. Acute kidney injury in acute liver failure: a review. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 701-712 [PMID: 24134153 DOI: 10.1586/17474124.2013.837264]
13 **Rognant N**. Acute kidney injury in patients with chronic liver disease. *World J Hepatol* 2015; **7**: 993-1000 [PMID: 25954481 DOI: 10.4254/wjh.v7.i7.993]
14 **Cabezuelo JB**, Ramírez P, Ríos A, Acosta F, Torres D, Sansano T, Pons JA, Bru M, Montoya M, Bueno FS, Robles R, Parrilla P. Risk factors of acute renal failure after liver transplantation. *Kidney Int* 2006; **69**: 1073-1080 [PMID: 16528257 DOI: 10.1038/sj.ki.5000216]
15 **Doi K**, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. *Kidney Int* 2016; **89**: 555-564 [PMID: 26880452 DOI: 10.1016/j.kint.2015.11.019]
16 **Lane K**, Dixon JJ, MacPhee IA, Philips BJ. Renohepatic crosstalk: does acute kidney injury cause liver dysfunction? *Nephrol Dial Transplant* 2013; **28**: 1634-1647 [PMID: 23685679 DOI: 10.1093/ndt/gft091]
17 **Mahmud N**. Selection for Liver Transplantation: Indications and Evaluation. *Curr Hepatol Rep* 2020; 1-10 [PMID: 32837824 DOI: 10.1007/s11901-020-00527-9]
18 **Line PD**, Dueland S. Liver transplantation for secondary liver tumours: The difficult balance between survival and recurrence. *J Hepatol* 2020; **73**: 1557-1562 [PMID: 32896581 DOI: 10.1016/j.jhep.2020.08.015]
19 **Leithead JA**, Rajoriya N, Gunson BK, Muiesan P, Ferguson JW. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. *J Hepatol* 2014; **60**: 1180-1186 [PMID: 24631601 DOI: 10.1016/j.jhep.2014.02.019]
20 **Leithead JA**, Armstrong MJ, Corbett C, Andrew M, Kothari C, Gunson BK, Muiesan P, Ferguson JW. Hepatic ischemia reperfusion injury is associated with acute kidney injury following donation after brain death liver transplantation. *Transpl Int* 2013; **26**: 1116-1125 [PMID: 24033747 DOI: 10.1111/tri.12175]
21 **Hashimoto K**, Miller C. The use of marginal grafts in liver transplantation. *J Hepatobiliary Pancreat Surg* 2008; **15**: 92-101 [PMID: 18392701 DOI: 10.1007/s00534-007-1300-z]
22 **Lee HT**, Park SW, Kim M, D'Agati VD. Acute kidney injury after hepatic ischemia and reperfusion injury in mice. *Lab Invest* 2009; **89**: 196-208 [PMID: 19079326 DOI: 10.1038/labinvest.2008.124]
23 **Robertson FP**, Yeung AC, Male V, Rahman S, Mallett S, Fuller BJ, Davidson BR. Urinary Neutrophil Gelatinase Associated Lipocalins (NGALs) predict acute kidney injury post liver transplant. *HPB (Oxford)* 2019; **21**: 473-481 [PMID: 30385051 DOI: 10.1016/j.hpb.2018.09.017]
24 **Kong HY**, Chen F, He Y, Wu LJ, Wang LQ, Zhu SM, Zheng SS. Intrarenal resistance index for the assessment of acute renal injury in a rat liver transplantation model. *BMC Nephrol* 2013; **14**: 55 [PMID: 23453043 DOI: 10.1186/1471-2369-14-55]
25 **Park SW**, Chen SW, Kim M, D'Agati VD, Lee HT. Human heat shock protein 27-overexpressing mice are protected against acute kidney injury after hepatic ischemia and reperfusion. *Am J Physiol Renal Physiol* 2009; **297**: F885-F894 [PMID: 19656912 DOI: 10.1152/ajprenal.00317.2009]
26 **Park SW**, Chen SW, Kim M, D'Agati VD, Lee HT. Selective intrarenal human A1 adenosine receptor overexpression reduces acute liver and kidney injury after hepatic ischemia reperfusion in mice. *Lab Invest* 2010; **90**: 476-495 [PMID: 20065944 DOI: 10.1038/labinvest.2009.143]
27 **Le Dorze M**, Legrand M, Payen D, Ince C. The role of the microcirculation in acute kidney injury. *Curr Opin Crit Care* 2009; **15**: 503-508 [PMID: 19829106 DOI: 10.1097/MCC.0b013e328332f6cf]
28 **Umbro I**, Tinti F, Scalera I, Evison F, Gunson B, Sharif A, Ferguson J, Muiesan P, Mitterhofer AP. Acute kidney injury and post-reperfusion syndrome in liver transplantation. *World J Gastroenterol* 2016; **22**: 9314-9323 [PMID: 27895419 DOI: 10.3748/wjg.v22.i42.9314]
29 **Mizota T**, Hamada M, Matsukawa S, Seo H, Tanaka T, Segawa H. Relationship Between Intraoperative Hypotension and Acute Kidney Injury After Living Donor Liver Transplantation: A Retrospective Analysis. *J Cardiothorac Vasc Anesth* 2017; **31**: 582-589 [PMID: 28216198 DOI: 10.1053/j.jvca.2016.12.002]

30 **Kandil MA**, Abouelenain KM, Alsebaey A, Rashed HS, Afifi MH, Mahmoud MA, Yassen KA. Impact of terlipressin infusion during and after live donor liver transplantation on incidence of acute kidney injury and neutrophil gelatinase-associated lipocalin serum levels: A randomized controlled trial. *Clin Transplant* 2017; **31** [PMID: 28564127 DOI: 10.1111/ctr.13019]

31 **Won YJ**, Kim HJ, Lim BG, Ahn HS, Hwang MH, Lee IO. Effect of Perioperative Terlipressin on Postoperative Renal Function in Patients Who Have Undergone Living Donor Liver Transplantation: A Meta-Analysis of Randomized Controlled Trials. *Transplant Proc* 2015; **47**: 1917-1925 [PMID: 26293074 DOI: 10.1016/j.transproceed.2015.06.023]

32 **Chae MS**, Lee N, Park DH, Lee J, Jung HS, Park CS, Choi JH, Hong SH. Influence of oxygen content immediately after graft reperfusion on occurrence of postoperative acute kidney injury in living donor liver transplantation. *Medicine (Baltimore)* 2017; **96**: e7626 [PMID: 28767577 DOI: 10.1097/MD.0000000000007626]

33 **Gonul Y**, Ozsoy M, Kocak A, Ozkececi ZT, Karavelioglu A, Bozkurt MF, Cartilli O, Keles I, Kocak H, Celik S. Antioxidant, Antiapoptotic and Inflammatory Effects of Interleukin-18 Binding Protein on Kidney Damage Induced by Hepatic Ischemia Reperfusion. *Am J Med Sci* 2016; **351**: 607-615 [PMID: 27238925 DOI: 10.1016/j.amjms.2016.02.017]

34 **Zhang W**, Wang M, Xie HY, Zhou L, Meng XQ, Shi J, Zheng S. Role of reactive oxygen species in mediating hepatic ischemia-reperfusion injury and its therapeutic applications in liver transplantation. *Transplant Proc* 2007; **39**: 1332-1337 [PMID: 17580134 DOI: 10.1016/j.transproceed.2006.11.021]

35 **Kadkhodaee M**, Mikaeili S, Zahmatkesh M, Golab F, Seifi B, Arab HA, Shams S, Mahdavi-Mazdeh M. Alteration of renal functional, oxidative stress and inflammatory indices following hepatic ischemia-reperfusion. *Gen Physiol Biophys* 2012; **31**: 195-202 [PMID: 22781823 DOI: 10.4149/gpb_2012_024]

36 **Luo C**, Yuan D, Li X, Yao W, Luo G, Chi X, Li H, Irwin MG, Xia Z, Hei Z. Propofol attenuated acute kidney injury after orthotopic liver transplantation *via* inhibiting gap junction composed of connexin 32. *Anesthesiology* 2015; **122**: 72-86 [PMID: 25254904 DOI: 10.1097/ALN.0000000000000448]

37 **Salama SA**, Kabel AM. Taxifolin ameliorates iron overload-induced hepatocellular injury: Modulating PI3K/AKT and p38 MAPK signaling, inflammatory response, and hepatocellular regeneration. *Chem Biol Interact* 2020; **330**: 109230 [PMID: 32828744 DOI: 10.1016/j.cbi.2020.109230]

38 **Quirk SM**, Hilbert JL, Fortune JE. Progesterone secretion by granulosa cells from rats with four- or five-day estrous cycles: the development of responses to follicle-stimulating hormone, luteinizing hormone, and testosterone. *Endocrinology* 1986; **118**: 2402-2410 [PMID: 3084218 DOI: 10.1038/s41467-019-09046-8]

39 **Sang BH**, Bang JY, Song JG, Hwang GS. Hypoalbuminemia Within Two Postoperative Days Is an Independent Risk Factor for Acute Kidney Injury Following Living Donor Liver Transplantation: A Propensity Score Analysis of 998 Consecutive Patients. *Crit Care Med* 2015; **43**: 2552-2561 [PMID: 26308436 DOI: 10.1097/CCM.0000000000001279]

40 **Lasheen NN**, Elayat WM, Elrefai MFM, Zaki WS, Ahmed EH, El Sheikh RMN, Abo Rayas DSA, Gad FRS. Possible role of garlic oil in ameliorating renal injury after liver ischemia/reperfusion in rats. *J Physiol Pharmacol* 2019; **70** [PMID: 32009629 DOI: 10.26402/jpp.2019.5.12]

41 **Seifi B**, Kadkhodaee M, Delavari F, Mikaeili S, Shams S, Ostad SN. Pretreatment with pentoxifylline and N-acetylcysteine in liver ischemia reperfusion-induced renal injury. *Ren Fail* 2012; **34**: 610-615 [PMID: 22364443 DOI: 10.3109/0886022X.2012.660827]

42 **Hu Z**, Zhang H, Yang SK, Wu X, He D, Cao K, Zhang W. Emerging Role of Ferroptosis in Acute Kidney Injury. *Oxid Med Cell Longev* 2019; **2019**: 8010614 [PMID: 31781351 DOI: 10.1155/2019/8010614]

43 **Vlahakos D**, Arkadopoulos N, Kostopanagiotou G, Siasiakou S, Kaklamanis L, Degiannis D, Demonakou M, Smyrniotis V. Deferoxamine attenuates lipid peroxidation, blocks interleukin-6 production, ameliorates sepsis inflammatory response syndrome, and confers renoprotection after acute hepatic ischemia in pigs. *Artif Organs* 2012; **36**: 400-408 [PMID: 22187937 DOI: 10.1111/j.1525-1594.2011.01385.x]

44 **Jegatheeswaran S**, Siriwardena AK. Experimental and clinical evidence for modification of hepatic ischaemia-reperfusion injury by N-acetylcysteine during major liver surgery. *HPB (Oxford)* 2011; **13**: 71-78 [PMID: 21241423 DOI: 10.1111/j.1477-2574.2010.00263.x]

45 **Khan AW**, Fuller BJ, Shah SR, Davidson BR, Rolles K. A prospective randomized trial of N-acetyl cysteine administration during cold preservation of the donor liver for transplantation. *Ann Hepatol* 2005; **4**: 121-126 [PMID: 16010245 DOI: 10.1016/s1665-2681(19)32075-7]

46 **Hilmi IA**, Peng Z, Planinsic RM, Damian D, Dai F, Tyurina YY, Kagan VE, Kellum JA. N-acetylcysteine does not prevent hepatorenal ischaemia-reperfusion injury in patients undergoing orthotopic liver transplantation. *Nephrol Dial Transplant* 2010; **25**: 2328-2333 [PMID: 20179007 DOI: 10.1093/ndt/gfq077]

47 **Zorov DB**, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev* 2014; **94**: 909-950 [PMID: 24987008 DOI: 10.1152/physrev.00026.2013]

48 **Chang HC**, Wu R, Shang M, Sato T, Chen C, Shapiro JS, Liu T, Thakur A, Sawicki KT, Prasad SV, Ardehali H. Reduction in mitochondrial iron alleviates cardiac damage during injury. *EMBO Mol Med* 2016; **8**: 247-267 [PMID: 26896449 DOI: 10.15252/emmm.201505748]

49 **Liu Q**, Krishnasamy Y, Rehman H, Lemasters JJ, Schnellmann RG, Zhong Z. Disrupted Renal

Mitochondrial Homeostasis after Liver Transplantation in Rats. *PLoS One* 2015; **10**: e0140906 [PMID: 26480480 DOI: 10.1371/journal.pone.0140906]

50 **Garrett SM**, Whitaker RM, Beeson CC, Schnellmann RG. Agonism of the 5-hydroxytryptamine 1F receptor promotes mitochondrial biogenesis and recovery from acute kidney injury. *J Pharmacol Exp Ther* 2014; **350**: 257-264 [PMID: 24849926 DOI: 10.1124/jpet.114.214700]

51 **Jesinkey SR**, Funk JA, Stallons LJ, Wills LP, Megyesi JK, Beeson CC, Schnellmann RG. Formoterol restores mitochondrial and renal function after ischemia-reperfusion injury. *J Am Soc Nephrol* 2014; **25**: 1157-1162 [PMID: 24511124 DOI: 10.1681/ASN.2013090952]

52 **Xie P**, Yang L, Talaiti A, Wu JJ, Yu J, Yu T, Wang HY, Huang B, Wu Q, Maimaitili Y, Wang J, Ma HP, Yang YN, Zheng H. Deferoxamine-activated hypoxia-inducible factor-1 restores cardioprotective effects of sevoflurane postconditioning in diabetic rats. *Acta Physiol (Oxf)* 2017; **221**: 98-114 [PMID: 28316125 DOI: 10.1111/apha.12874]

53 **Zhang X**, Du P, Luo K, Li Y, Liu Z, Wang W, Zeng C, Ye Q, Xiao Q. Hypoxia-inducible factor-1alpha protects the liver against ischemia-reperfusion injury by regulating the A2B adenosine receptor. *Bioengineered* 2021; **12**: 3737-3752 [PMID: 34288817 DOI: 10.1080/21655979.2021.1953217]

54 **Ju C**, Wang M, Tak E, Kim B, Emontzpohl C, Yang Y, Yuan X, Kutay H, Liang Y, Hall DR, Dar WA, Bynon JS, Carmeliet P, Ghoshal K, Eltzschig HK. Hypoxia-inducible factor-1α-dependent induction of miR122 enhances hepatic ischemia tolerance. *J Clin Invest* 2021; **131** [PMID: 33792566 DOI: 10.1172/JCI140300]

55 **Selten JW**, Verhoeven CJ, Heedfeld V, Roest HP, de Jonge J, Pirenne J, van Pelt J, Ijzermans JNM, Monbaliu D, van der Laan LJW. The release of microRNA-122 during liver preservation is associated with early allograft dysfunction and graft survival after transplantation. *Liver Transpl* 2017; **23**: 946-956 [PMID: 28388830 DOI: 10.1002/lt.24766]

56 **Verhoeven CJ**, Farid WRR, de Ruiter PEE, de Jonge J, Kwekkeboom J, Metselaar HJ, Tilanus HW, van der Lann LJW, Kazemier G. MicroRNAs in preservation solution are more predictive of graft quality than their expression in liver tissue. *Liver Transplantation* 2012; **18**: S36

57 **Bezinover D**, Kadry Z, McCullough P, McQuillan PM, Uemura T, Welker K, Mastro AM, Janicki PK. Release of cytokines and hemodynamic instability during the reperfusion of a liver graft. *Liver Transpl* 2011; **17**: 324-330 [PMID: 21384515 DOI: 10.1002/lt.22227]

58 **Lu TF**, Yang TH, Zhong CP, Shen C, Lin WW, Gu GX, Xia Q, Xu N. Dual Effect of Hepatic Macrophages on Liver Ischemia and Reperfusion Injury during Liver Transplantation. *Immune Netw* 2018; **18**: e24 [PMID: 29984042 DOI: 10.4110/in.2018.18.e24]

59 **Baggiolini M**, Clark-Lewis I. Interleukin-8, a chemotactic and inflammatory cytokine. *FEBS Lett* 1992; **307**: 97-101 [PMID: 1639201 DOI: 10.1016/0014-5793(92)80909-z]

60 **Su L**, Li N, Tang H, Lou Z, Chong X, Zhang C, Su J, Dong X. Kupffer cell-derived TNF-α promotes hepatocytes to produce CXCL1 and mobilize neutrophils in response to necrotic cells. *Cell Death Dis* 2018; **9**: 323 [PMID: 29476069 DOI: 10.1038/s41419-018-0377-4]

61 **Robertson FP**, Goswami R, Wright GP, Imber C, Sharma D, Malago M, Fuller BJ, Davidson BR. Remote ischaemic preconditioning in orthotopic liver transplantation (RIPCOLT trial): a pilot randomized controlled feasibility study. *HPB (Oxford)* 2017; **19**: 757-767 [PMID: 28651898 DOI: 10.1016/j.hpb.2017.05.005]

62 **Lee SY**, Kim DH, Sung SA, Kim MG, Cho WY, Kim HK, Jo SK. Sphingosine-1-phosphate reduces hepatic ischaemia/reperfusion-induced acute kidney injury through attenuation of endothelial injury in mice. *Nephrology (Carlton)* 2011; **16**: 163-173 [PMID: 21272128 DOI: 10.1111/j.1440-1797.2010.01386.x]

63 **Koo A**, Komatsu H, Tao G, Inoue M, Guth PH, Kaplowitz N. Contribution of no-reflow phenomenon to hepatic injury after ischemia-reperfusion: evidence for a role for superoxide anion. *Hepatology* 1992; **15**: 507-514 [PMID: 1312056 DOI: 10.1002/hep.1840150325]

64 **Ohkohchi N**. Mechanisms of preservation and ischemic/reperfusion injury in liver transplantation. *Transplant Proc* 2002; **34**: 2670-2673 [PMID: 12431569 DOI: 10.1016/s0041-1345(02)03370-5]

65 **Polat C**, Tokyol C, Kahraman A, Sabuncuoğlu B, Yìlmaz S. The effects of desferrioxamine and quercetin on hepatic ischemia-reperfusion induced renal disturbance. *Prostaglandins Leukot Essent Fatty Acids* 2006; **74**: 379-383 [PMID: 16698257 DOI: 10.1016/j.plefa.2006.03.007]

66 **Arai M**, Thurman RG, Lemasters JJ. Ischemic preconditioning of rat livers against cold storage-reperfusion injury: role of nonparenchymal cells and the phenomenon of heterologous preconditioning. *Liver Transpl* 2001; **7**: 292-299 [PMID: 11303287 DOI: 10.1053/jlts.2001.23080]

67 **Rao J**, Lu L, Zhai Y. T cells in organ ischemia reperfusion injury. *Curr Opin Organ Transplant* 2014; **19**: 115-120 [PMID: 24576906 DOI: 10.1097/MOT.0000000000000064]

68 **Song P**, Zhang J, Zhang Y, Shu Z, Xu P, He L, Yang C, Wang H, Li Y, Li Q. Hepatic recruitment of CD11b+Ly6C+ inflammatory monocytes promotes hepatic ischemia/reperfusion injury. *Int J Mol Med* 2018; **41**: 935-945 [PMID: 29251315 DOI: 10.3892/ijmm.2017.3315]

69 **Oliveira THC**, Marques PE, Proost P, Teixeira MMM. Neutrophils: a cornerstone of liver ischemia and reperfusion injury. *Lab Invest* 2018; **98**: 51-62 [PMID: 28920945 DOI: 10.1038/labinvest.2017.90]

70 **Rampes S**, Ma D. Hepatic ischemia-reperfusion injury in liver transplant setting: mechanisms and protective strategies. *J Biomed Res* 2019; **33**: 221-234 [PMID: 32383437 DOI: 10.7555/JBR.32.20180087]

71 **Pulitano C**, Ho P, Verran D, Sandroussi C, Joseph D, Bowen DG, McCaughan GW, Crawford M,

Shackel N. Molecular profiling of postreperfusion milieu determines acute kidney injury after liver transplantation: A prospective study. *Liver Transpl* 2018; **24**: 922-931 [PMID: 29684255 DOI: 10.1002/lt.25178]

72 **Dinarello CA**, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 binding protein. *Front Immunol* 2013; **4**: 289 [PMID: 24115947 DOI: 10.3389/fimmu.2013.00289]

73 **Gonul Y**, Kazandı S, Kocak A, Ahsen A, Bal A, Karavelioglu A, Hazman O, Turamanlar O, Kokulu S, Yuksel S. Interleukin-18 Binding Protein Pretreatment Attenuates Kidney Injury Induced by Hepatic Ischemia Reperfusion. *Am J Med Sci* 2016; **352**: 200-207 [PMID: 27524219 DOI: 10.1016/j.amjms.2016.04.012]

74 **Hetz H**, Bauer M, Lahner D, Faybik P, Winning J, Ankersmit HJ, Bacher A, Krenn CG. Endothelin activation and postoperative renal failure after human liver transplantation. *Liver Transpl* 2005; **11**: 1201-1206 [PMID: 16184572 DOI: 10.1002/lt.20477]

75 **Gandhi CR**, Kang Y, De Wolf A, Madariaga J, Aggarwal S, Scott V, Fung J. Altered endothelin homeostasis in patients undergoing liver transplantation. *Liver Transpl Surg* 1996; **2**: 362-369 [PMID: 9346677 DOI: 10.1002/lt.500020506]

76 **Lladó L**, Ramos E, Figueras J, Serrano T, Torras J, Rafecas A, Fabregat J, Lama C, Busquets J, Dalmau A, Sabaté A, Jaurrieta E. Influence of endothelin-1 on hemodynamics during liver transplantation with and without temporary portocaval shunt: results of a clinical randomized study. *Liver Transpl* 2002; **8**: 27-33 [PMID: 11799482 DOI: 10.1053/jlts.2002.30338]

77 **Panchal HJ**, Durinka JB, Patterson J, Karipineni F, Ashburn S, Siskind E, Ortiz J. Survival outcomes in liver transplant recipients with Model for End-stage Liver Disease scores of 40 or higher: a decade-long experience. *HPB (Oxford)* 2015; **17**: 1074-1084 [PMID: 26373873 DOI: 10.1111/hpb.12485]

78 **Rabelink TJ**, Kaasjager KA, Boer P, Stroes EG, Braam B, Koomans HA. Effects of endothelin-1 on renal function in humans: implications for physiology and pathophysiology. *Kidney Int* 1994; **46**: 376-381 [PMID: 7967349 DOI: 10.1038/ki.1994.284]

79 **Kohan DE**, Inscho EW, Wesson D, Pollock DM. Physiology of endothelin and the kidney. *Compr Physiol* 2011; **1**: 883-919 [PMID: 23737206 DOI: 10.1002/cphy.c100039]

80 **Choi YJ**, Zhou D, Barbosa ACS, Niu Y, Guan X, Xu M, Ren S, Nolin TD, Liu Y, Xie W. Activation of Constitutive Androstane Receptor Ameliorates Renal Ischemia-Reperfusion-Induced Kidney and Liver Injury. *Mol Pharmacol* 2018; **93**: 239-250 [PMID: 29351922 DOI: 10.1124/mol.117.111146]

81 **Wu S**, Yao W, Chen C, Chen H, Huang F, Liu Y, Cai J, Yuan D, Hei Z. Connexin 32 deficiency protects the liver against ischemia/reperfusion injury. *Eur J Pharmacol* 2020; **876**: 173056 [PMID: 32147436 DOI: 10.1016/j.ejphar.2020.173056]

82 **Capalbo O**, Giuliani S, Ferrero-Fernández A, Casciato P, Musso CG. Kidney-liver pathophysiological crosstalk: its characteristics and importance. *Int Urol Nephrol* 2019; **51**: 2203-2207 [PMID: 31549285 DOI: 10.1007/s11255-019-02288-x]

83 **Gardner DS**, De Brot S, Dunford LJ, Grau-Roma L, Welham SJ, Fallman R, O'Sullivan SE, Oh W, Devonald MA. Remote effects of acute kidney injury in a porcine model. *Am J Physiol Renal Physiol* 2016; **310**: F259-F271 [PMID: 26608790 DOI: 10.1152/ajprenal.00389.2015]

84 **Chen SW**, Park SW, Kim M, Brown KM, D'Agati VD, Lee HT. Human heat shock protein 27 overexpressing mice are protected against hepatic ischemia and reperfusion injury. *Transplantation* 2009; **87**: 1478-1487 [PMID: 19461484 DOI: 10.1097/TP.0b013e3181a3c691]

85 **Park SW**, Kim M, Kim JY, Ham A, Brown KM, Mori-Akiyama Y, Ouellette AJ, D'Agati VD, Lee HT. Paneth cell-mediated multiorgan dysfunction after acute kidney injury. *J Immunol* 2012; **189**: 5421-5433 [PMID: 23109723 DOI: 10.4049/jimmunol.1200581]

86 **Han SJ**, Li H, Kim M, D'Agati V, Lee HT. Intestinal Toll-like receptor 9 deficiency leads to Paneth cell hyperplasia and exacerbates kidney, intestine, and liver injury after ischemia/reperfusion injury. *Kidney Int* 2019; **95**: 859-879 [PMID: 30777286 DOI: 10.1016/j.kint.2018.10.035]

87 **Perel P**, Roberts I, Sena E, Wheble P, Briscoe C, Sandercock P, Macleod M, Mignini LE, Jayaram P, Khan KS. Comparison of treatment effects between animal experiments and clinical trials: systematic review. *BMJ* 2007; **334**: 197 [PMID: 17175568 DOI: 10.1136/bmj.39048.407928.BE]

88 **Brekke TD**, Steele KA, Mulley JF. Inbred or Outbred? *G3 (Bethesda)* 2018; **8**: 679-686 [PMID: 29242387 DOI: 10.1534/g3.117.300495]

89 **Francoz C**, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol* 2010; **52**: 605-613 [PMID: 20185192 DOI: 10.1016/j.jhep.2009.11.025]

90 **MacDonald AJ**, Nadim MK, Durand F, Karvellas CJ. Acute kidney injury in cirrhosis: implications for liver transplantation. *Curr Opin Crit Care* 2019; **25**: 171-178 [PMID: 30676329 DOI: 10.1097/MCC.0000000000000590]

91 **Yeung ACY**, Morozov A, Robertson FP, Fuller BJ, Davidson BR. Neutrophil Gelatinase-Associated Lipocalin (NGAL) in predicting acute kidney injury following orthotopic liver transplantation: A systematic review. *Int J Surg* 2018; **59**: 48-54 [PMID: 30273683 DOI: 10.1016/j.ijsu.2018.09.003]

92 **Kuehn EW**, Hirt MN, John AK, Muehlenhardt P, Boehlke C, Pütz M, Kramer-Zucker AG, Bashkurov M, van de Weyer PS, Kotsis F, Walz G. Kidney injury molecule 1 (Kim1) is a novel ciliary molecule and interactor of polycystin 2. *Biochem Biophys Res Commun* 2007; **364**: 861-866 [PMID: 18273441 DOI: 10.1016/j.bbrc.2007.10.103]

93 **Dedeoglu B**, de Geus HR, Fortrie G, Betjes MG. Novel biomarkers for the prediction of acute kidney injury in patients undergoing liver transplantation. *Biomark Med* 2013; **7**: 947-957 [PMID: 24266830 DOI: 10.2217/bmm.13.91]

94 **Bao GH**, Ho CT, Barasch J. The Ligands of Neutrophil Gelatinase-Associated Lipocalin. *RSC Adv*

2015; **5**: 104363-104374 [PMID: 27617081 DOI: 10.1039/C5RA18736B]

95 **Bao G**, Clifton M, Hoette TM, Mori K, Deng SX, Qiu A, Viltard M, Williams D, Paragas N, Leete T, Kulkarni R, Li X, Lee B, Kalandadze A, Ratner AJ, Pizarro JC, Schmidt-Ott KM, Landry DW, Raymond KN, Strong RK, Barasch J. Iron traffics in circulation bound to a siderocalin (Ngal)-catechol complex. *Nat Chem Biol* 2010; **6**: 602-609 [PMID: 20581821 DOI: 10.1038/nchembio.402]

96 **Cassidy H**, Slyne J, Higgins M, Radford R, Conlon PJ, Watson AJ, Ryan MP, McMorrow T, Slattery C. Neutrophil gelatinase-associated lipocalin (NGAL) is localised to the primary cilium in renal tubular epithelial cells - A novel source of urinary biomarkers of renal injury. *Biochim Biophys Acta Mol Basis Dis* 2019; **1865**: 165532 [PMID: 31422117 DOI: 10.1016/j.bbadis.2019.165532]

97 **Han WK**, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int* 2002; **62**: 237-244 [PMID: 12081583 DOI: 10.1046/j.1523-1755.2002.00433.x]

98 **Han SJ**, Jang HS, Seu SY, Cho HJ, Hwang YJ, Kim JI, Park KM. Hepatic ischemia/reperfusion injury disrupts the homeostasis of kidney primary cilia *via* oxidative stress. *Biochim Biophys Acta Mol Basis Dis* 2017; **1863**: 1817-1828 [PMID: 28495528 DOI: 10.1016/j.bbadis.2017.05.004]

99 **Spasic M**, Jacobs CR. Primary cilia: Cell and molecular mechanosensors directing whole tissue function. *Semin Cell Dev Biol* 2017; **71**: 42-52 [PMID: 28843978 DOI: 10.1016/j.semcdb.2017.08.036]

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2022 January 25; 11(1): 30-38

DOI: 10.5527/wjn.v11.i1.30

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Retrospective Study

Unilateral hypoplastic kidney in adults: An experience of a tertiary-level urology center

Rabea Ahmed Gadelkareem, Nasreldin Mohammed

ORCID number: Rabea Ahmed Gadelkareem 0000-0003-4403-2859; Nasreldin Mohammed 0000-0002-0232-9497.

Author contributions: Gadelkareem RA designed the research, searched and collected the data, and wrote the paper; Mohammed N contributed to study design and manuscript writing and revision, and supervised the work; both authors approved the paper.

Institutional review board statement: This study was approved on November 25, 2021 by the Medical Ethics Committee of the Faculty of Medicine, Assiut University, Egypt as a topic in a research project titled "Experience of a tertiary-level urology center in the clinical urological events of rare and very rare incidence: a retrospective research project." The institutional review board number is 17300684.

Informed consent statement: This article is a retrospective one with only descriptive anonymous data. Patients were not required to give informed consent to the study because the manipulated data were anonymous and were obtained after each patient agreed to treatment by consent.

Conflict-of-interest statement: The

Rabea Ahmed Gadelkareem, Nasreldin Mohammed, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Assiut 71515, Egypt

Corresponding author: Rabea Ahmed Gadelkareem, MD, Associate Professor, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Elgamaa Street, Assiut 71515, Egypt. dr.rabeagad@yahoo.com

Abstract

BACKGROUND

Unilateral small-sized kidney is a radiological term referring to both the congenital and acquired causes of reduced kidney volume. However, the hypoplastic kidney may have peculiar clinical and radiological characterizations.

AIM

To evaluate the clinical presentations, complications, and management approaches of the radiologically diagnosed unilateral hypoplastic kidney.

METHODS

A retrospective review of the records of patients with a radiological diagnosis of unilateral hypoplastic kidney between July 2015 and June 2020 was done at Assiut Urology and Nephrology Hospital, Assiut University, Egypt.

RESULTS

A total of 33 cases were diagnosed to have unilateral hypoplastic kidney with a mean (range) age of 39.5 ± 11.2 (19-73) years. The main clinical presentation was loin pain (51.5%), stone passer (9.1%), anuria (12.1%), accidental discovery (15.2%), or manifestations of urinary tract infections (12.1%). Computed tomography was the most useful tool for radiological diagnosis. However, radioisotope scanning could be requested for verification of surgical interventions and nephrectomy decisions. Urolithiasis occurred in 23 (69.7%) cases and pyuria was detected in 22 (66.7%) cases where the infection was documented by culture and sensitivity test in 19 cases. While the non-complicated cases were managed by assurance only (12.1%), nephrectomy (15.2%) was performed for persistent complications. However, symptomatic (27.3%) and endoscopic (45.6%) approaches were used for the management of correctable complications.

CONCLUSION

Unilateral hypoplastic kidney in adults has various complications that range from

authors have no financial relationships to disclose.

Data sharing statement: No additional data are available. All the processed data are included in the study.

Country/Territory of origin: Egypt

Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 26, 2021
Peer-review started: March 26, 2021
First decision: July 31, 2021
Revised: August 7, 2021
Accepted: December 21, 2021
Article in press: December 21, 2021
Published online: January 25, 2022

P-Reviewer: Arguelles E
S-Editor: Liu M
L-Editor: Wang TQ
P-Editor: Liu M

urinary tract infections to death from septicemia. Diagnosis is mainly radiological and management is usually conservative or minimally invasive.

Key Words: Congenital anomalies; Hypoplastic kidney; Kidney size; Small sized kidney; Solitary kidney; Urolithiasis

Core Tip: The study reviewed the clinical characteristics, complications, and management of the unilateral hypoplastic kidney in adults. The various clinical presentations are due to the different complications including urolithiasis, obstruction, urinary tract infections (UTIs), and life-threatening morbidities such as anuria and septicemia. Renal radioisotope scanning is indicated for cases with sizable kidneys, verification of the decision of surgical intervention, and patient preference. Conservative and endoscopic approaches should be tried first for the management of complications. However, laparoscopic nephrectomy is recommended for the treatment of persistent complications such as hypertension and recurrent UTIs or urolithiasis.

Citation: Gadelkareem RA, Mohammed N. Unilateral hypoplastic kidney in adults: An experience of a tertiary-level urology center. *World J Nephrol* 2022; 11(1): 30-38
URL: https://www.wjgnet.com/2220-6124/full/v11/i1/30.htm
DOI: https://dx.doi.org/10.5527/wjn.v11.i1.30

INTRODUCTION

The term "small-sized kidney" is an imaging-based description that defines the reduction of the kidney mass or volume[1]. It could be unilateral or bilateral, where the latter form is associated with the progression of chronic kidney disease through its different stages[2,3]. However, the unilateral small-sized kidney usually presents clinically with normal total renal functions due to the normal and, in many instances, compensating contralateral kidney[4,5]. It results from many contributing pathological entities such as congenital hypoplasia, chronic pyelonephritis, renovascular ischemia, and urological interventions and surgeries[6]. The hypoplastic kidney is a main contributing factor for this entity and is predominantly unilateral with acquired contralateral compensatory hypertrophy. Although the secreted urine in these kidneys may have normal constituents, its amount is low with subsequent urinary stasis. So, the hypoplastic kidney predisposes to urinary tract infections (UTIs) and urolithiasis. Its share in the total renal function is, definitely, lower than the other kidney down to warrant surgical removal, when indicated, without significant effect on the patient's total renal function. Hypoplastic dysplastic kidney could be confused with the chronic pyelonephritic kidney which results from repeated attacks of ascending infections. However, the etiology of the hypoplastic kidney is mostly attributed to developmental arrest due to ischemia during embryogenesis[7,8]. Our aim was to study the clinical presentations, radiological differences between the congenital and acquired causes, indications and lines of surgical intervention, and patient's perception of treatment.

MATERIALS AND METHODS

Study design

A retrospective search of the manual and electronic patients' records in our hospital was done for the patients who had a diagnosis of unilateral congenital small-sized kidney or hypoplasia between July 2015 and June 2020. Demographic variables including age and gender were studied. Also, clinical variables including the clinical presentations, laboratory and imaging investigations, complications, and management were studied. Patients' perception of the diagnosis that they had low function kidneys was traced in the records of their counseling and subsequent follow-up compliance according to the decision of management.

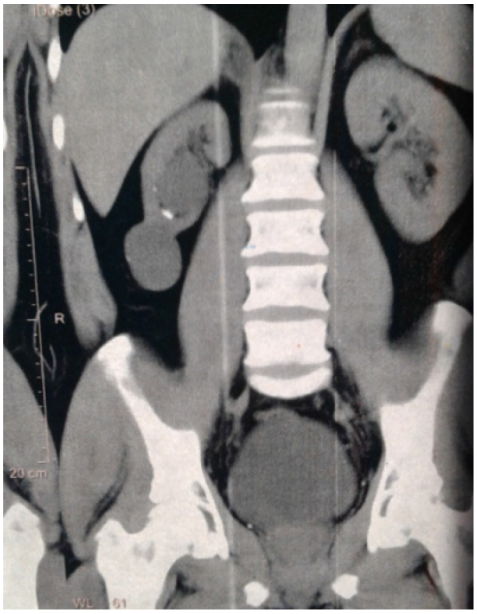

Figure 1 A 44-year-old male patient presented with right loin pain due to right hypoplastic kidney. A coronal view of non-contrast multi-slice computed tomography of the abdomen and pelvis showing the small-sized right kidney with a smooth outline, two simple cysts at the middle and lower poles, and a very small stone in the lower calyx. This case was managed conservatively.

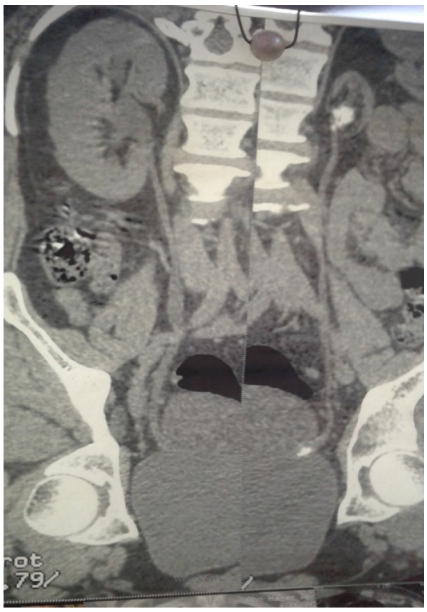

Figure 2 A 43-year-old male patient presented with irritative lower urinary tract symptoms due to a left hypoplastic kidney complicated by stones. A coronal view of non-contrast multi-slice computed tomography of the abdomen and pelvis showing the severely diminutive left kidney with non-obstructing stones in the renal pelvis and left intramural ureter. This case was managed by left ureteroscopy and nephrectomy.

Owing to the difficult differentiation between the hypoplastic kidney and atrophic causes of the unilateral small-sized kidney which could be accurately done only by histopathological studying, we employed the radiological features for the definition of the hypoplastic kidney as a kidney with smooth outline contour without strands in the surrounding fat (Figure 1), a length less than 9 cm or 3-vertebra height, or a glomerular filtration rate less than 40% of a total function that is not less than 60 mL/min/1.73 m^2. Patients who had documented acquired causes for the unilateral small-sized kidney including a previous treatment of urolithiasis by surgeries or extracorporeal shock wave lithotripsy, evidence of previous normal kidney size, previous partial nephrectomy, and vesicoureteral reflux disease were excluded from the study.

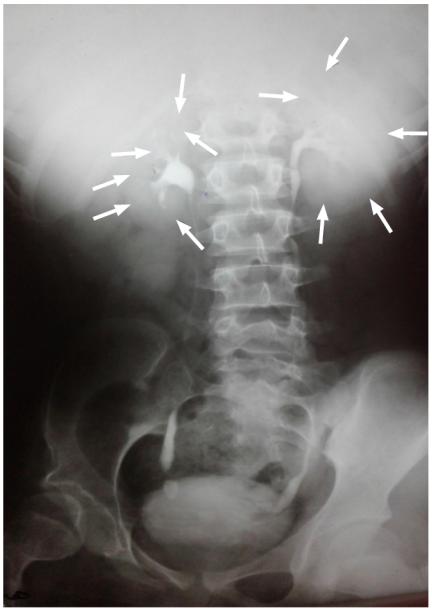

Figure 3 A 39-year-old female patient presented with right loin pain due to right hypoplastic kidney. An intravenous urography film showing the right hypoplastic kidney with preservation of the normal shape of the pelvicalyceal system and fine details of the whole kidney without obstruction, despite the presence of a right lower ureteral stone. Note the difference between the sizes of both kidneys that are outlined by the arrows.

Biostatistics

The data were descriptive and were presented as numbers and percentages or mean ± standard deviation. No biostatistician revision was warranted.

RESULTS

Thirty-three patients were included in the study. The demographic and clinical characteristics are summarized in Table 1.

Ultrasonography and plain radiography were routine imaging tools. However, computed tomography (CT) was the best tool for the characterization of the morphological features and complications (Table 2) (Figures 1 and 2). Intravenous urography was performed in two patient (Figure 3). Radioisotope scanning was performed for a limited number of cases (Table 3).

Urolithiasis was the most common complication of the hypoplastic kidney (Table 4). One patient died from septicemia due to obstructive pyelonephritis of the contralateral kidney after 2 years from the original diagnosis.

Different treatment approaches were used, including nephrectomy, endoscopic treatment of stones, conservative and symptomatic treatment, and assurance only for the cases without complications. Laparoscopic nephrectomy was performed in five cases for treatment of uncontrolled hypertension or persistent UTIs (Table 5).

All patients expressed concerns about the effect on the total kidney function. They had been educated that the lesion was unilateral and should not lead to end-stage renal disease. Four patients without complications preferred to have objective confirmation of the condition by renal radioisotope scanning including two potential kidney donors who were excluded from the donation (Table 3).

Follow-up duration varied between 7-56 mo. Three cases suffered from recurrent UTIs after stone removal and were managed conservatively.

DISCUSSION

The incidence of the small-sized kidney is variable in clinical settings[9]. Common causes of the unilateral small-sized kidney include chronic pyelonephritis, reflux or obstructive renal atrophy, and renovascular ischemia followed by the uncommon causes represented as congenital renal hypoplasia, tuberculosis, and partial nephrectomy[6]. The unilateral small-sized kidney which results from chronic pyelonephritis, congenital hypoplasia, or both represents a clinical difficulty[9].

Table 1 Demographic and clinical characteristics of the patients (*n* = 33), *n* (%)

Variable	Value
Age (yr)	
Mean ± SD	39.5 ± 11.2
Median (range)	40 (19-73)
Gender	
Male	19 (57.6)
Female	14 (42.4)
Main clinical presentations	
Ipsilateral loin pain	8 (24.2)
Contralateral loin pain	4 (12.1)
Bilateral or vague abdominal pain	5 (15.2)
UTI manifestations	4 (12.1)
Stone passer ± LUTS or colic	3 (9.1)
Anuria/oliguria	4 (12.1)
Accidental discovery F[1]	5 (15.2)
Anatomical side	
Right	23 (69.7)
Left	10 (30.3)
Laboratory investigations	
Serum creatinine mean ± SD; median (range) (mg/dL)	1.2 ± 0.68; 0.9 (0.66-3.6)
Positive for protein in urine	5 (15.2)
Patients with WBCs > 10/HPF in urine F[2]	22 (66.7)
Patients with RBCs > 3/HPF in urine	15 (45.5)

[1]F: Two cases of them were potential living donors and were excluded due to this anomaly and the other three cases were investigated for hypertension.
[2]F: In these cases, positive culture and sensitivity tests were reported in 19 cases (86.4%). HPF: High power field; LUTS: Lower urinary tract symptoms; RBCs: Red blood corpuscles; UTI: Urinary tract infection; WBCs: White blood cells.

Congenital anomalies of the urinary system are usually detected during childhood. However, when the lesion is commonly unilateral such as the hypoplastic kidney, it can pass unnoticed until the accidental discovery or development of complications in adulthood[10]. The common clinical presentations are related to the underlying complications of the hypoplastic kidney such as urolithiasis, recurrent UTIs, and hypertension[6,8]. Other rare presentations include vaginal dribbling due to ectopic ureteral insertion in females[11]. In the current study, loin pain was a cardinal presentation that refers either to the high incidence of complications including urolithiasis, hydronephrosis, and UTIs or the compensatory effect of the contralateral kidney[4-6,8].

Imaging represents a fundamental role in the urological practice with prompt advances through the last decades. Kidney size is a significant predictor of its function. Also, it is a cardinal item in urinary imaging and evaluation of the total renal functions. Bilateral reduction of renal size is imperatively associated with chronic renal impairment, especially with glomerulonephritis and other systemic parenchymal medical disorders[2,3].

Kidney size or volume and length are significant indicators for its function and affecting diseases. Measurement of the size of the kidney according to the old imaging modalities was two-dimensional and expressed relative to the corresponding vertebral heights such as in the plain and excretory radiographs[12]. However, many imaging modalities have been evolved and used recently for the measurement of three-dimensional kidney size. Among these modalities, ultrasonography has been the most practically used one, because it is available, simple, non-invasive, and repeatable. The

Table 2 Number of patients and abnormal findings (other than small-sized kidney) per imaging tool, *n* (%)

Imaging modality	Number of patients who had this imaging	Abnormal findings	*n* (%)
US	33 (100)	Stones	19 (57.6)
		Cysts	3 (9.1)
		Hydronephrosis	7 (21.2)
KUB	33 (100)	Stones	18 (54.6)
IVU	2 (6.1)	Hydronephrosis	1 (3)
MSCT	27 (81.8)	Stones	23 (69.7)
		Cysts	3 (9.1)
		Hydronephrosis	8 (24.2)

IVU: Intravenous urography; KUB: Kidney-ureter-bladder radiography; MSCT: Multi-slice computed tomography; US: Ultrasonography.

Table 3 Total and split renal functions represented by the glomerular filtration rate in patients who were evaluated by renal isotope scanning (*n* = 8), *n* (%)

Case No.	Age (yr)	Gender	GFR (mL/min/1.73 m^2)			Indication for isotope scanning
			Total	Right	Left	
Case 1	25	Male	92.4	61.9 (67)	30.5 (33)	Kidney donation
Case 2	42	Female	83.2	53.4 (64.2)	29.8 (35.8)	Kidney donation
Case 3	47	Female	88.5	67.8 (76.6)	20.7 (23.4)	To verify decision
Case 4	45	Female	69.7	61.2 (87.8)	8.5 (12.2)	Patient request
Case 5	21	Female	86	16.8 (19.5)	69.2 (80.5)	Patient request
Case 6	37	Male	77.6	58.2 (75)	19.4 (25)	To verify decision
Case 7	28	Male	83.4	17.5 (21)	65.9 (79)	To verify decision
Case 8	26	Male	66.8	7.5 (11.2)	59.3 (88.8)	To verify decision

Table 4 Rates of complications that occurred in patients with unilateral hypoplastic kidney (*n* = 29/33), *n* (%)

Complication	Number of patients	Involvement/localization		
		Ipsilateral	Contralateral	Bilateral/systemic
Urolithiasis	23 (69.7)	12 (36.4)	3 (9.1)	8 (24.2)
Renal cysts	3 (9.1)	2 (6.1)	1 (3)	0 (0)
Hydronephrosis	8 (24.2)	3 (9.1)	4 (12.1)	1 (3)
Recurrent UTI	10 (30.3)	1 (3)	2 (6.1)	7 (21.2)
Hypertension	3 (9.1)	NA	NA	3 (9.1)
Septicemia	1 (3)	0 (0)	1 (3)	1 (3)

NA: Not applicable; UTI: Urinary tract infection.

length and size of the kidney correlate and are usually expressed relative to the whole body anthropometric measures. Size is more accurately expressed as volume by three dimensions which are length, width, and thickness with approximate mean values of 12 cm, 6 cm, and 3 cm, respectively. In spite of the absence of consensus about the definite normal values of renal dimensions among the different populations, renal length is a reproducible, accurate, and more valuable tool for studying renal diseases in adults[12-14]. Accordingly, and in parallel to these established findings, the imaging-based definition was considered in the current study. The need for

Table 5 Management approaches for patients with unilateral hypoplastic kidney (*n* = 33), *n* (%)

Approach of management	Category/variety	*n* (%)
Assurance only		4 (12.1)
Conservative/symptomatic treatment F[1]	Total number of patients who received the treatment F[1]	9 (27.3)
	For hypertension	2 (6.1)
	For UTI	3 (9.1)
	For stones	5 (15.2)
	Hydronephrosis	1 (3)
	For cysts	1 (3)
Shock wave lithotripsy		8 (24.2)
	Ipsilateral	2 (6.1)
	Contralateral	5 (15.2)
	Bilateral	1 (3)
Endoscopic procedures		
	Ipsilateral ureteroscopy	3 (9.1)
	Contralateral ureteroscopy	3 (9.1)
	Contralateral JJ placement	5 (15.2)
Laparoscopic nephrectomy		5 (15.2)
	For recurrent UTI	2 (6.1)
	For hypertension	3 (9.1)
Open nephrectomy		1 (3)
	For stones	1 (3)

[1]F: Many patients received conservative treatment for more than one element of complications, while others received it for certain complications and, at the same time, received surgical interventions for other complications. Also, some patients had failed conservative treatment before surgical interventions. JJ: Double-J ureteral stent; UTI: Urinary tract infection.

documentation of the reduction of renal function was warranted only in patients with a relatively minimal size reduction, verification of the interventional management including nephrectomy, and patient insistence on numerical documentation of function. Otherwise, the severe reduction in kidney size and signs of compensation of the contralateral kidney were enough to settle the management decision in most of the cases.

Radiographic features of the uncomplicated hypoplastic kidney include a smooth outer contour of the kidney with a reduced number of calyces without caliceal clubbing or dilatation. However, these features, especially the caliceal morphology, could be disturbed in complicated cases such as urolithiasis and UTIs. These changes may concern its morphological differentiation from the atrophied kidney due to chronic pyelonephritis with an irregular contour and clubbed or dilated calyces due to scarring of the parenchyma which exerts traction forces between the renal surface and the caliceal cavity[6,8]. Renal radioisotope scanning is a tool for accurate and numerical evaluation of renal function[15]. Also, the resistive index by Doppler ultrasound showed a favorable sensitivity in the differentiation of the atrophied and hypoplastic kidneys[16]. In the current study, the indicators of the acquired affection were used to exclude patients with those findings from the study.

In cases of uncomplicated congenital hypoplastic kidney, no symptoms or therapeutic interventions are warranted. However, the management of hypoplastic kidneys is usually directed to the complications rather than the anomaly itself[10]. Indications for nephrectomy include hypertension, recurrent infections, and urolithiasis. In our series, nephrectomy was mainly done for hypertension in relatively young patients, whatever was the degree of hypertension. In the old patients, nephrectomy was preserved for those patients who had uncontrolled hypertension or those who received multiple drugs of more than one antihypertensive drug group for

control. Stone passer and UTIs were other indications for surgical removal of the hypoplastic kidney.

Advantages of this series include its presentation in the time that the clinical studying of the clinical entity of hypoplastic kidney in adults has become scarce in the literature[10]. Also, it presented the classic clinical setting of the hypoplastic kidney with the patients' perception of the potential implications of the disease. Moreover, it provided the clinical experience of a high-volume center and a tertiary level urology hospital with wide geographical drainage of urological disorders. Retrospective studying may not allow an ideal design for studying. However, it is the most suitable form for rare conditions.

CONCLUSION

In conclusion, unilateral small-sized kidney in adults is a radiological diagnosis. The hypoplastic kidney is a contributing pathology with various clinical presentations due to the development of complications. Although routine imaging by abdominal ultrasonography and radiography is available, abdominal CT is commonly indicated due to complications. In the current study, renal radioisotope scanning was indicated for relatively sizable kidneys, verification of the decision of surgical intervention, and patient request for confirmation of the lesion. The unilateral small-sized kidney is commonly being complicated by urolithiasis, obstruction, or UTIs resulting in more aggressive and life-threatening morbidities such as anuria and septicemia. Endoscopic interventions are mainly for the management of urolithiasis. While conservative management is commonly planned for this lesion, interventional management approaches including nephrectomy are mainly performed for treatment of the complications such as hypertension and recurrent UTIs or urolithiasis.

ARTICLE HIGHLIGHTS

Research background

Unilateral small-sized kidney is a radiological term referring to both the congenital and acquired causes of reduced kidney volume. However, the hypoplastic kidney may have peculiar clinical and radiological characteristics. Its symptomatic clinical presentations are mostly attributed to the occurrence of underlying complications warranting early and proper management.

Research motivation

There is a noticeable lack of research on the clinical aspects of the unilateral hypoplastic kidney in the updated literature. Presentation of the current series may help enrich the literature and enhance the practice.

Research objectives

To study the clinical characteristics, complications, and management approaches of the unilateral radiologically diagnosed hypoplastic kidney in adults.

Research methods

A retrospective study was carried out on patients with a radiological diagnosis of unilateral hypoplastic kidney between July 2015 and June 2020 at a tertiary-level urology center in Egypt. The demographic, clinical, and radiological characteristics and management approaches were reviewed.

Research results

The study included 33 cases with unilateral hypoplastic kidney with a mean (range) age of 39.5 ± 11.2 (19-73) years. Loin pain (51.5%) was the main clinical presentation followed by the accidental discovery (15.2%), anuria (12.1%), manifestations of urinary tract infections (UTIs; 12.1%), and stone passer (9.1%). Radiological diagnosis was commonly done by CT showing the main features including the small volume and the preserved smooth outline and structures. Urolithiasis occurred in 23 (69.7%) cases and pyuria was detected in 22 (66.7%) cases where UTIs were documented by culture and sensitivity test in 19 cases. The non-complicated cases were managed by assurance only (12.1%), symptomatic (27.3%) and endoscopic (45.6%) approaches were used for

the management of simple and correctable complications, and nephrectomy (15.2%) was performed for persistent complications.

Research conclusions

There are various presentations for the unilateral hypoplastic kidney ranging from accidental discovery to UTIs that may lead to death by septicemia. The diagnosis is mainly radiological and management is usually conservative or minimally invasive relative to the underlying findings.

Research perspectives

Presentation of the clinical characteristics and outcomes may enhance the relevant urological practice of this disease. Urologists can provide the proper management including the conservative approaches for the simple complications and laparoscopic nephrectomy for the persistent complications.

REFERENCES

1 **Yazici R**, Guney İ, Altintepe L, Yazici M. Does the serum uric acid level have any relation to arterial stiffness or blood pressure in adults with congenital renal agenesis and/or hypoplasia? *Clin Exp Hypertens* 2017; **39**: 145-149 [PMID: 28287880 DOI: 10.1080/10641963.2016.1210630]

2 **Matsell DG**, Cojocaru D, Matsell EW, Eddy AA. The impact of small kidneys. *Pediatr Nephrol* 2015; **30**: 1501-1509 [PMID: 25794549 DOI: 10.1007/s00467-015-3079-5]

3 **El-Reshaid K**, El-Reshaid W, Al-Bader D, Varro J, Madda J, Sallam HT. Biopsy of small kidneys: A safe and a useful guide to potentially treatable kidney disease. *Saudi J Kidney Dis Transpl* 2017; **28**: 298-306 [PMID: 28352011 DOI: 10.4103/1319-2442.202767]

4 **Rojas-Canales DM**, Li JY, Makuei L, Gleadle JM. Compensatory renal hypertrophy following nephrectomy: When and how? *Nephrology (Carlton)* 2019; **24**: 1225-1232 [PMID: 30809888 DOI: 10.1111/nep.13578]

5 **Wang MK**, Gaither T, Phelps A, Cohen R, Baskin L. The Incidence and Durability of Compensatory Hypertrophy in Pediatric Patients with Solitary Kidneys. *Urology* 2019; **129**: 188-193 [PMID: 30986483 DOI: 10.1016/j.urology.2019.04.003]

6 **Neiman HL**, Korsower JM, Reeder MM. Unilateral small kidney. *JAMA* 1977; **238**: 971-972 [PMID: 577993]

7 **MATHE CP**. The diminutive kidney; congenital hypoplasia and atrophic pyelonephritis. *Calif Med* 1956; **84**: 110-114 [PMID: 13284642]

8 **Ramanathan S**, Kumar D, Khanna M, Al Heidous M, Sheikh A, Virmani V, Palaniappan Y. Multi-modality imaging review of congenital abnormalities of kidney and upper urinary tract. *World J Radiol* 2016; **8**: 132-141 [PMID: 26981222 DOI: 10.4329/wjr.v8.i2.132]

9 **Bengtsson C**, Hood B. The unilateral small kidney with special reference to the hypoplastic kidney. Review of the literature and authors' points of view. *Int Urol Nephrol* 1971; **3**: 337-351 [PMID: 4949479 DOI: 10.1007/BF02082282]

10 **Xiao GQ**, Jerome JG, Wu G. Unilateral hypoplastic kidney and ureter associated with diverse mesonephric remnant hyperplasia. *Am J Clin Exp Urol* 2015; **3**: 107-111 [PMID: 26309900]

11 **Bozorgi F**, Connolly LP, Bauer SB, Neish AS, Tan PE, Schofield D, Treves ST. Hypoplastic dysplastic kidney with a vaginal ectopic ureter identified by technetium-99m-DMSA scintigraphy. *J Nucl Med* 1998; **39**: 113-115 [PMID: 9443748]

12 **Emamian SA**, Nielsen MB, Pedersen JF, Ytte L. Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers. *AJR Am J Roentgenol* 1993; **160**: 83-86 [PMID: 8416654 DOI: 10.2214/ajr.160.1.8416654]

13 **Glodny B**, Unterholzner V, Taferner B, Hofmann KJ, Rehder P, Strasak A, Petersen J. Normal kidney size and its influencing factors - a 64-slice MDCT study of 1.040 asymptomatic patients. *BMC Urol* 2009; **9**: 19 [PMID: 20030823 DOI: 10.1186/1471-2490-9-19]

14 **Musa MJ**, Abukonna A. Sonographic measurement of renal size in normal high altitude Populations. *J Radiat Res Appl Sci* 2017; **10**: 178-182 [DOI: 10.1016/j.jrras.2017.04.004]

15 **Ul Hassan M**, Khan SH, Ashraf M, Najar S, Shaheen F. (99m)Tc Diethylenetriaminepentacetic Acid Angiotension-coverting Enzyme Inhibitor Renography as Screening Test for Renovascular Hypertension in Unilateral Small Kidney: A Prospective Study. *World J Nucl Med* 2014; **13**: 159-162 [PMID: 25538486 DOI: 10.4103/1450-1147.144815]

16 **Dalkiran T**, Kandur Y, Dagoglu B, Saki H, Gungor S, Ipek S. The comparison of the resistivity index values in the ultrasonographic evaluation of a unilateral atrophic/hypoplastic kidney. *Ren Fail* 2020; **42**: 289-293 [PMID: 32208786 DOI: 10.1080/0886022X.2020.1743720]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com